PLAN INTEGRATION

Phase I	***Phase II***	***Phase III***
Strategy		
Define BTP & Realign Treatment Algorithm	*Rapid & Reliable Treatment for BTP*	*Patient and Payer Satisfaction*
Critical Success Factor		
• Authoritative treatment guidelines that recognize BTP and ROO as preferred treatment • Comprehensive HEOR support for treatment of BTP with ROO	• Value proposition of ROO established in treatment of BTP • FEBT value proposition embraced by key managed market decision markers (*outcomes* + *price* + *contracts*)	• Coordinated pull-through program that optimizes managed care opportunity • Efficient prescriber support overcomes prior authorization barriers
Tactic		
1) Advisory Boards 2) Validate guidelines 3) Customer Pricing Study 4) Retrospective Study of BTP Treatment (assess burden of BTP) 5) Establish ROO in literature 6) Conduct clinical trial ROO vs. SAO 7) Establish validated chronic pain assessment tool which includes BTP component 8) Conduct HEOR initiatives	1) Phase IIIB/IV: FEBT vs. retrospective data 2) Petition USP for ROO classification 3) MSLs conduct formulary review discussions 4) HEOR impact model 5) "Cost of Pain" speakers program 6) Managed care selling materials (eg, Dossier, FEBT Slide Kit) 7) Advisory board meetings	1) Pull-though programs 2) Prior authorization and medical necessity support program, office staff training program 3) Provider advisory boards 4) AMCP exhibits and educational programs 5) Call center initiatives 6) Continued patient support (Emerging Solutions in Pain) to encourage appropriate and safe use of FEBT

Appendix 3 – FEBT Development Plan

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I. Summary

Indication(s); Breakthrough Pain in Cancer Patients (BTP-C), Breakthrough Pain in Noncancer Patients (BTP-NC)

Filing Dates: US NDA – August 2005 (BTP-C), US sNDA – 3Q '06 (BTP-NC), EU MAA – TBD

Clinical Status: Phase III BTP-C

Launch Timing: 3Q '06 (BTP-C), 4Q ' 07 (BTP-NC)

Manufacturing: API; Johnson Matthey, Formulation and packaging; Salt Lake City (CIMA Eden Prairie secondary facility)

Key Project Issues and Risks: Negotiation of Risk Management Plan, timely recruitment of patients for open-label study (99-15), launch timing following approval. Launch concurrent with Barr generic ACTIQ® entry.

In August 2004, Cephalon acquired CIMA LABS INC. (CIMA) and with the acquisition the OraVescent® fentanyl (FEBT) technology. FEBT is the registered trademark name for the oral transmucosal drug delivery system developed by CIMA. FEBT is patent protected. The United States patent estate protecting FEBT brand oral transmucosal fentanyl citrate comprises issued patent US 6,200,604, expiring March 26, 2019, and 6 filed pending patent applications. Additional patent protection for methods of manufacturing and packaging comprises U.S. 6,155,423, expiring April 1, 2018, and 3 filed pending patent applications.

The unique FEBT formulation contains bicarbonate which produces effervescence when placed in the mouth. The release of carbon dioxide acts as an absorption enhancer. The carbon dioxide reduces the thickness of the mucosal layer, opens tight junctions, increases hydrophobicity of the cell membrane, and gradually changes the pH of the microenvironment which facilitates absorption through the mucosa. Fentanyl, which is a poorly soluble weak base, has limited oral bioavailability (<33%) from the gut wall metabolism and extensive hepatic metabolism. The rapid and more complete absorption through the oral mucosal provided by the FEBT technology increases the potential for the dosage form to perform better than traditional oral dosage forms. Additionally, FEBT may have inherent advantages over the existing ACTIQ® oral transmucosal fentanyl product. FEBT should be easier for the patient to use, may reduce user error, and have higher bioavailability, allowing for lower doses to be effective compared to ACTIQ®. The absence of the stick allows the patient to avoid the stigma and eliminates the "lollipop" look that has raised concerns regarding pediatric exposure with ACTIQ®.

At the time of the acquisition, the Phase III efficacy and safety trials for FEBT were in progress. The clinical trials supported label claims identical to the existing ACTIQ® label. With the knowledge of the breakthrough pain (BTP) market, a 2-phase approach to development and regulatory submission is being executed for FEBT. The first phase of the strategy is to file an NDA for the FEBT dosage form with an indication to manage BTP in opioid-tolerant patients with cancer, followed by submission of a sNDA for an indication to manage BTP in opioid-tolerant patients with chronic noncancer pain. The initial filing would include the existing studies initiated by CIMA and an additional efficacy study to evaluate onset of analgesia. Four additional Phase I studies to characterize the pharmacokinetics, bioavailability, and support titration schemes will be conducted and included in the initial NDA. The studies necessary for an expanded indication in BTP associated with chronic, noncancer pain will be initiated in the first quarter of 2005, with the intent of having an sNDA ready for filing upon approval of the original NDA in 3Q '06. This time

line provides the noncancer BTP data available to address medical inquiries near the launch of the product with the breakthrough cancer pain indication.

On October 16, 2003, CIMA and Taiho executed a Development and License Option Agreement. On July 31, 2004, a Data Access Agreement between CIMA and Taiho was signed for CIMA to conduct Phase I studies to support the Japanese registration. The Phase I studies are being conducted in the United States in Japanese nationals. The subsequent studies required for registration will be conducted by Taiho in Japan. Cephalon will review Taiho's protocols to ensure they also support Cephalon's interests.

II. FEBT Target Product Profile

Indication

First indication: For the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

Expanded indication: FEBT is indicated only for the management of breakthrough pain (BTP) in patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain.

Contraindications, Warnings, and Precautions

- Same as ACTIQ® except for pediatric and diabetic warnings and disposal instructions, which are not expected for this formulation.
- May have warnings about tampering with the formulation and misuse.

Pharmacokinetics

- Absorption information based on relative/absolute Bioavailability Study.
- The PK data (C_{max}, AUC, and t_{max}) on proposed marketing strengths of 100, 200, 400, and 800 mcg will be described within a table.
- In the studies conducted with FEBT and ACTIQ® the t_{max}, for ACTIQ® was ~2 hours, while for FEBT it was 45 minutes. This is with venous sampling. T_{max} with arterial sampling will also be included in the label. T_{max} with arterial sampling is what is in current ACTIQ® label. In the label, the t_{max} for FEBT will be included, but the ACTIQ® t_{max} will most likely not be in the label.

Clinical Trials

- Study 099-014, Efficacy of FEBT in opioid-tolerant cancer patients with BTP
  - Proportion of patients achieving a "successful" dose
  - Distribution of patients by successful dose
  - Result from $SPID_{0-30}$
  - Graph of PID over time (15, 30, 45, 60 minutes)
- Study 3039, Efficacy of FEBT in opioid-tolerant cancer patients with BTP
  - Proportion of patients achieving a "successful" dose
  - Distribution of patients by successful dose (may combine with previous study)
  - Result from $SPID_{0-60}$
  - Graph of PID over time (5, 10, 15, 30, 45, 60, 90, 120 minutes)
  - Onset of meaningful pain relief is within 30 minutes for the majority of patients.

Safety

- AE profile similar to ACTIQ®
- Number of opioid-tolerant cancer patients studied (~500)
- Average duration of treatment in Open Label Extension Study (099-15)
- AE table from the titration phases of 099-014, 3039, and new patients in 099-015
- AE table from long-term Open Label study (099-15)

> AE table from switching study after the switch from ACTIQ® to FEBT

Special Populations

> Pharmacokinetic and adverse event information in patients with mucositis with any AE information

Dosage and Administration

See Appendix I for full proposed DOSING AND ADMINISTRATION section of FEBT package insert.

> All patients need to be opioid tolerant.

> Patients should start on 100 mcg with the exception of patients previously receiving ACTIQ® at doses >600 mcg.

> In adult patients previously receiving ACTIQ® for BTCP, the initial episode dose of FEBT should be as shown in the table below:

Current ACTIQ® dose (µg) per BTCP Episode	FEBT Initial Titration Dose (µg)
200	100
400	100
600	100
800	200
1200	400
1600	600

> Dose titration instructions will be similar to those of ACTIQ®.

- Place tablet between upper cheek and gum.
- Should take 15 minutes to dissolve – can be swallowed if not completely dissolved after 30 minutes. Rub cheek area over the unit if the unit is not dissolved fully after 15 minutes.
- Don't drink or eat while in mouth.
- If excessive signs of opioid effects appear – spit out.
- Swallowing may result in lower peak concentrations.
- Redosing within a single episode:
  - 30 minutes after start of previous tablet
  - Second dose should not exceed initial dose level.
- Increasing the dose:
  - The dose should only be increased to the next higher dosage level until the patient reaches a dose that provides adequate analgesia for a BTCP episode.
  - Dosage strengths should not be skipped.
  - Multiple tablets may be used to produce mcg equivalents to available doses.
  - Evaluate dose over several episodes (1 to 2 days)

- Side effects more frequent during this initial titration phase

- Daily limit:
  - Treat four or fewer episodes per day.

III. Regulatory Strategy

CIMA filed IND 65447 for FEBT citrate in July 2002. A pre-IND meeting was conducted with the FDA in November 2001. An End of Phase II meeting was conducted in December 2003. Ownership of the IND was formally transferred from CIMA to Cephalon, Inc. in October 2004.

The NDA for FEBT will be submitted in August 2005 for a BTP indication in opioid-tolerant patients with cancer. A pre-NDA meeting for the first submission is planned for April 2005. The safety data on 500 unique patient exposures with 50% of these receiving higher doses (>600 mcg) requested by FDA will be included in the initial NDA submission.

The NDA will include a complete Quality section to support the novel FEBT dosage form. To support continuity of product supply, 2 manufacturing and primary packaging sites will be submitted. The 2 facilities are Eden Prairie, Minnesota, and Salt Lake City, Utah.

In September 2004, Cephalon conducted an End of Phase II meeting with the FDA to discuss expanding the ACTIQ® indication to include managing BTP in opioid-tolerant patients with chronic noncancer pain. The label expansion will be pursued for FEBT. The working premise is that the agreements with FDA regarding ACTIQ® will apply directly to FEBT. Cephalon will request confirmation of those agreements from the FDA relative to an expanded label for FEBT. The expanded label will be filed as a sNDA once the NDA has been approved. It will contain data from a 12-month safety study and 2 efficacy studies. The FDA has requested that the submission contain 300 to 500 noncancer patients treated for 6 months and 100 patients treated for 1 year. This must be part of the sNDA at the time of submission and cannot be submitted at a later update.

A critical component of the development, approval, and commercialization of FEBT is the Risk Management Program (RMP). While it is likely that the RMP for FEBT will, similar to ACTIQ®, focus on preventing/minimizing (1) abuse and diversion, (2) accidental ingestion (primarily by children), and (3) improper patient selection (opioid–non-tolerant patients), it is also likely that, given the characteristics inherent in FEBT and the heightened external concerns about opioid-prescribing, the RMP will focus more significantly on abuse and diversion issues, with less focus on accidental ingestion. Further, given the recent FDA Risk MAP guidance, it is expected that the RMP will have more areas where the Company is expected to provide the Agency with measurable data on risk-minimization activities. Therefore, while the RMP will continue to focus on prevention, education, monitoring, and intervention (also similar to the ACTIQ® RMP), there will be significantly more focus on measuring the success of the RMP. Agency guidance will be sought at the upcoming pre-NDA meeting, and it is expected that negotiations on the particulars of the RMP will continue throughout the approval process.

IV. Preclinical Development

At the September 2004 End of Phase II meeting with the FDA to discuss an indication for noncancer BTP, Cephalon requested concurrence from the agency that the ACTIQ® toxicology data, currently included under NDA 20-747, are adequate to support the proposed indication noting that NDA 20-747 is a 505(b)(2) application referencing Duragesic's NDA 19-813 that is not supported by a carcinogenicity study. It is expected that FDA response regarding ACTIQ® is relevant to the FEBT NDA and sNDA which will be confirmed at the appropriate FDA meetings for both cancer and noncancer BTP. For the adult population, the FDA encouraged Cephalon to conduct fertility/reproduction studies in male rats (Segment I), pre- and postnatal development

study (Segment III), and 2-year carcinogenicity studies in 2 species. In the meeting and documented in the minutes, Cephalon stated that they understood that carcinogenicity studies were encouraged but not required. FDA stated that carcinogenicity studies would probably be necessary to support extension of the new indication into a population of pediatric patients without malignancies. At this time, Cephalon has no definitive plans to conduct these studies for inclusion in the initial NDA for BTP in cancer patients nor the subsequent sNDA for noncancer pain BTP.

V. Clinical Development Plan

As described previously, the Clinical Program will support a cancer and a noncancer BTP indication filed in 2 separate regulatory submissions.

At an End of Phase II meeting for ACTIQ® in noncancer BTP, the FDA communicated the requirement for full ICH guideline safety exposure, specifically in the noncancer patient population. The time to recruit and treat for the 1-year exposure requirement does not allow for a single NDA containing the required data for an indication in both populations to be submitted in time to ensure approval prior to generic entry for ACTIQ®. Hence, to facilitate approval of the NDA prior to generic entry, the BTP in cancer patients will be filed first in August 2005. To maximize commercial opportunity, the noncancer BTP studies will be initiated in 1Q '05, with the data available to file an sNDA after initial approval, and available to address medical inquiries near the launch of the product with the breakthrough cancer pain indication.

The current ACTIQ® labeling describes the t_{max} for fentanyl occurring between 20 and 40 minutes. Arterial plasma sampling was done in the ACTIQ® studies that generated these data. Subsequent pharmacokinetic data generated for ACTIQ® and FEBT has used venous sampling. The t_{max} from these subsequent studies has been generally greater than 50 minutes, with the head-to-head comparison studies containing both FEBT and ACTIQ®, revealing t_{max} values of 2 hours for ACTIQ® and 1 hour for FEBT. These discrepancies reveal the importance of describing within the labeling the source of the plasma samples in order to understand the differences in t_{max} between the ACTIQ® label and the eventual FEBT label. As part of the labeling changes for the sugar-free formulation of ACTIQ®, a clarifying statement explaining that the PK parameters are from arterial sampling should be added to the ACTIQ® label. A similar statement should be included in the eventual FEBT labeling. In addition, publications of the FEBT PK studies evaluating both ACTIQ® and FEBT will be useful in pointing out that FEBT is actually faster than ACTIQ® in reaching t_{max}. The following sections outline the clinical studies to support each indication and tables mapping target promotional claims to the specific studies which will support those claims. Appendix 2 contains a more detailed overview of the clinical studies.

Breakthrough Cancer Pain Clinical Program

The first NDA for BTP in opioid-tolerant cancer patients will include results from 6 clinical pharmacology trials and 4 clinical safety and efficacy trials. The FDA has requested that there be 500 unique patient exposures with 50% of these receiving higher doses (>600 mcg).

Study	Population	Treatments(s)	N	Primary Objective(s)	Primary Outcome	FPFV	Results Available
099-11 – Dose Proportionality	Healthy volunteers	FEBT 270, 810, 1080, 1300 mcg ACTIQ® 1600	42	Establish the PK profile of FEBT	C_{max}, AUC, t_{max}	---	Complete
099-18 – Dose Proportionality	Healthy volunteers	FEBT 200, 500, 810 mcg	27	Determine if dose strengths proportional	C_{max} AUC	---	Complete
1028 – Absolute/ Relative Bioavailability	Healthy volunteers	FEBT 800, ACTIQ® 800, Fentanyl Inj, Fentanyl PO Sol.	24	Determine the absolute and relative bioavailability of fentanyl delivered via FEBT	AUC	1Q '05	2Q '05
1026 – BE of multiple lower doses vs. higher ones	Healthy volunteers	FEBT 100 and 400 mcg	24	4x100 mcg is equivalent to 1x400 mcg	C_{max}, AUC, t_{max}	1Q '05	2Q '05
1029 – Multiple Dose PK	Healthy volunteers	FEBT 400 mcg	24	Determine the steady state (ss) kinetics of FEBT	C_{maxss} and C_{minss}	1Q '05	2Q '05
1027 – Dose Proportionality	Healthy volunteers	FEBT 100, 200, 400, 800 mcg	24	Determine the PK characteristics of doses and show proportionality	C_{max} and AUC	1Q '05	4Q '05
099-16 – Safety	Cancer patients with mucositis	FEBT 200 mcg	18	Determine if PK of FEBT is altered in this population	C_{max}, AUC, t_{max}	4Q '04	2Q '05
099-14 – Efficacy	BTP cancer	FEBT and PBO	120	Determine the efficacy of FEBT	SPID $_{0-30}$	2Q '04	1Q '05
099-15 – Open Label 12-month Safety	BTP cancer	FEBT 100-800 mcg	400	Safety	Safety	2Q '04	2Q '05
3039 – Onset of Analgesia	BTP cancer	FEBT and PBO	100	Determine the efficacy of FEBT	SPID $_{0-60}$	1Q '05	2Q '05

Noncancer BTP Clinical Program

The sNDA for BTP in opioid-tolerant patients in a broad population will include 3 clinical studies, 2 efficacy studies and 1 open-label safety study. The 2 efficacy studies have similar design but 2 different populations. One study will recruit patients with low back pain; the second study will recruit patients with neuropathic pain from varied origin. The safety study will enroll patients with a variety of pain etiologies.

Study	Population	Treatments(s)	N	Primary Objective	Primary Outcome	FPFV	Results Available
3041 Efficacy Study	BTP – neuropathic pain	FEBT and PBO	100	Determine the efficacy of FEBT	SPID 0-60	3Q '05	2Q '06
3042 – Efficacy Study	BTP – low back pain	FEBT and PBO	100	Determine the efficacy of FEBT	SPID 0-60	3Q '05	2Q '06
3040 – 12-mo Open-Label Safety Study	BTP – chronic noncancer pain	FEBT	750	Safety	Safety	1Q '05	3Q '06

Supportive Studies

Several Outcome studies are being discussed for market support in the broader indication.

Study	Population	Treatments(s)	N	Primary Objective(s)	Primary Outcome	FPFV	Results Available
Health Economics	Chronic pain	FEBT and Percocet		Determine the efficacy FEBT has better patient outcomes	Function		
Efficacy	Chronic pain	FEBT, Percocet, and PBO		Determine the duration of effect for FEBT	Time with >50% rescue		
Efficacy	Chronic pain	FEBT and MSIR		Relative analgesic efficacy	SPID		

Studies for Taiho

CIMA is under contract to conduct the following Phase I studies to support the Japanese Registration Program. The Phase 1 studies will be conducted in the United States in Japanese nationals. The subsequent studies required for registration will be conducted by Taiho.

Study	Population	Treatments(s)	N	Primary Objective(s)	Primary Outcome	FPFV	Results Available
099-19 – PK	Healthy Japanese	FEBT 100, 200,	28	Establish the PK profile of FEBT in	C_{max}, AUC,	3Q	4Q '04

profile	volunteers	400, 800		Japanese volunteers	t_{max}	'04	
099-20 – MD PK	Healthy Japanese volunteers	FEBT 200 and 400 mcg	20	MD PK profile of FEBT in Japanese volunteers	C_{maxss}	4Q '04	2Q '05
099-21 – PK of Sequential dosing	Healthy Japanese volunteers	FEBT 200 and 400 mcg	20	PK profile of giving 2 doses FEBT simultaneously or sequentially	C_{max} and AUC	1Q '05	3Q '06

Additional Studies to Be Developed

- Consistency of plasma levels compared with ACTIQ®
- Duration of analgesia in chronic pain
- Relative potency
- Abuse liability
- Tampering
- Studies to support Risk Management Program

Clinical Studies Time Lines

Indication for BTP in Cancer				
Study	Protocol	FPFV	LPLV	Results
099-11 – Dose Proportionality	Jul 03	July 03	Aug 03	Sep 03
099-18 – Dose Proportionality	Oct 03	Nov 03	Dec 03	Mar 04
099-14 – Efficacy	Jul 03	Jul 03	Jan 05	Mar 05
099-15 – Open Label 12-Month Safety	Oct-03	Nov 03	May 06	Jun 05
099-16 – Safety Mucositis	Oct 04	Jan 04	Apr 05	Jun 05
3039 – Onset of Analgesia	Nov 04	Jan 04	May 05	Jun 05
1027 – Dose Proportionality	Nov 04	Jan 05	Jan 05	Apr 05
1028 – Absolute Bioavailability	Dec 04	Jan 05	Feb 05	Apr 05
1029 – MD PK	Dec 04	Feb 05	Mar 05	May 05
1026 – BE of Multiple Lower Doses vs Higher Ones	Jan 05	Mar 05	Apr 05	Jun 05

Expanded Indication for BTP in Noncancer				
Study	Protocol	FPFV	LPLV	Results
3040 – 12-mo Open-Label Safety	Nov 04	Feb 05	Jun 06	Jul 06
3041 – NPP	Jan 05	Mar 05	Sep 05	
3042 – LBP	Jan 05	Mar 05	Sep 05	
Studies Supporting Taiho				
Study	Protocol	FPFV	LPLV	Results
099-19 – PK	-	3Q '04	4Q '04	4Q '04
099-20 – MD PK	Nov 04	1Q '05		
099-21 – PK Sequential Dosing	Feb 05	1Q '05		

Target Promotional Claims and Associated Studies

The following tables map the target claims to the specific clinical studies which support those claims:

Target Claims at the Time of First Launch – BTP in Cancer Patients

Claim	Supportive Study	Outcome Variable	Vehicle
FEBT is effective in managing BTP in opioid-tolerant cancer patients	099-14 – Cancer Efficacy 3039 – Cancer Efficacy	SPID-$_{0\text{-}30}$, Graph of PID over 60 min	Label
Time of analgesic onset with FEBT is <15 minutes	3039 – Cancer Efficacy	Stopwatch† and PID at 5 and 10 min*	Label*/ Promotional†
Time between BTP episodes after treatment with FEBT was on average >6 hrs while the time between events after treatment with PBO was less	099-14 – Cancer Efficacy 3039 – Cancer Efficacy	Time between BTP episodes	Promotional
FEBT is superior to PBO in controlling pain through 2 hours	3039 – Cancer Efficacy	PID scores through 2 hours postdose	Label

Claim	Supportive Study	Outcome Variable	Vehicle
There is dose proportionality among the dose strengths.	Dose proportionality Studies 099-18 and 1027	C_{max} and AUC values	Label
After 1 year of treatment with FEBT xx% of patients continued to achieve good pain control	099-15 – Cancer Safety Study	Global evaluation of efficacy	Promotional
Patients switching from ACTIQ® to FEBT should be placed on 1 dose below half the ACTIQ® dose (ie, 800 ACTIQ® is 200 FEBT)	1028 – Absolute Bioavailability Study 099-15 – Cancer Safety 3039 – Cancer Efficacy	Safety and efficacy observed after switching paradigm employed C_{max} and AUC values	Label
Of the patients switched from ACTIQ® to FEBT xx% required a dose increase, yy% required a dose decrease and zz% required no further adjustment in dose	3039 – Cancer Efficacy 099-15 – Cancer Safety Study	Dose of FEBT at the time of randomization in DB phase	Label
The majority (xx%) of patients preferred FEBT over previous BTP medication.	3039 – Cancer Efficacy 99-015 – Cancer Safety Study	Preference questionnaire administered at the end of the study	Promotional

Target Claims at the Time of the Second Launch With Expanded Indication

Claim	Supportive Study	Outcome Variable	Vehicle
FEBT is effective in managing BTP in opioid-tolerant chronic noncancer pain patients	3041 – NPP efficacy 3042 – LBP efficacy	$SPID_{0-60}$, graph of PID over 60 min	Label
Time of analgesic onset with FEBT is <15 minutes	3041 – NPP efficacy 3042 – LBP efficacy	Stopwatch† and PID at 5 and 10 min*	Label*/ Promotional†
Time between BTP episodes after treatment with FEBT was on average >6 hrs while the time between them after treatment with PBO was less	3041 – NPP efficacy 3042 – LBP efficacy	Time between BTP episodes	Promotional
FEBT is superior to PBO in controlling pain through 2 hours	3041 – NPP efficacy 3042 – LBP efficacy	PID scores through 2 hours postdose	Label
After 12 months of use xx% of patients still able to achieve adequate pain relief with FEBT	3049 – Open-Label Safety in chronic noncancer pain	% of patients still in study	Promotional

Additional Claims Desired

Claim	Supportive Study	Outcome Variable	Vehicle
The relative potency of FEBT to MSIR is 1:10-20	TBD	PID, pupil diameter	Publication
The duration of analgesic effect of FEBT is 6 hours	Patients with chronic OA pain	PID, PR, time to rescue	Publication
FEBT has less of a dwell time than ACTIQ®	TBD		

VI. Health Economics (HECON)

Objective: To provide economic justification and differentiation for FEBT vs competitors

> HECON measures are included in Noncancer Open-Label study (3040)
> Finalize HECON strategy for Noncancer BTP by Q2 '05

Challenges

- Reimbursement / Managed care
  - Increasing barriers anticipated
  - Generics
  - Unarticulated needs
- Need to bridge ACTIQ to FEBT

Opportunities

- Rapid onset
- Cross-functional pricing and reimbursement infrastructure
- Malignant + nonmalignant pain

Objectives	Tactic/Program*	Target Audience	Timing	Resource
P&RE issues identification	Input into P&RE Assessment	Brand	Q2 '05	Market Research HEOR RE
Value generation	Input into long-term safety study David Nash – Thomas Jefferson research Patient preference	Clinicians Managed care	Q4 '04 Initiate planning Q1 '05	HEOR Clinical Research Sci Comm Marketing Publications
Managed care support	Partnership/ Phase IV studies? Formulary kit/tools	Managed care Clinicians	Initiate planning Q2 '05	HEOR Marketing Clinical Research Prof Services

VII. Pharmaceutical Development

Drug Product Development Plan

The dosage form is designed using the proprietary FEBT technology. The formulation contains bicarbonate which produces effervescence when placed in the mouth. The release of carbon dioxide acts as an absorption enhancer. The carbon dioxide reduces the thickness of the mucosal layer, opens tight junctions, increases hydrophobicity of the cell membrane, and gradually changes the pH of the microenvironment, which facilitates absorption through the mucosa. Fentanyl, which is a poorly soluble weak base, has limited oral bioavailability (<33%) because of gut wall metabolism and extensive hepatic metabolism. The rapid and more complete absorption through the oral mucosal provided by the FEBT technology increases the potential for the dosage form to perform better than traditional oral dosage forms.

Five commercial doses (100, 200, 400, 600, and 800 mcg) were developed. In December 2003, 2 batches of each strength were manufactured at the Brooklyn Park Facility. The material was used to support clinical trials, and stability was initiated for all strengths by February 1, 2004. The batch size of 100,000 tablets represents greater than one-tenth scale of the purposed commercial batch size in the Eden Prairie, Minnesota facility. The 12-month stability data on these batches will be included in the August 2005 NDA submission.

In December 2004, site registration batches will be manufactured at the Eden Prairie facility. One full-scale 80-kg batch of each strength was manufactured, packaged, and placed on stability by January 2005.

In early 2005, site registration batches will be manufactured at the Salt Lake City, Utah, facility. One 22-kg scale batch of each strength will be manufactured, packaged, and placed on stability. Three-month stability data on these batches will be included in the August 2005 NDA submission.

All of the development batches were compressed with plain tooling. The commercial product will be debossed on 1 side with the Cephalon logo and a single digit representing strength on the opposite side.

Package Development Plan

The physical characteristics of the FEBT formulation require a high moisture-vapor barrier. The friability of the tablet requires proprietary handling technology to transfer the tablets from the tablet press to the packaging line, and prohibits the use of push-through blister package designs. These factors led to unit dose foil blister package materials with a peel-opening design.

The API fentanyl is a Class II narcotic with a high toxicity level, and requires child-resistant (CR) packaging. The intent is for the CR package to meet the F1 child-resistance level. The patient population for this product necessitates a package design that will concurrently comply with the senior-friendly protocol.

Several prototype opening designs were developed and tested for CR. The 3 passing designs were tested in Market Research focus groups with the intent to optimize a package that meets F1 and senior-friendly protocols. The proposed design is a 2X2 bend and peel blister card. The card achieved a 96% child-effectiveness rating and a 97% senior-effectiveness rating. Opening instructions which are concise and readily understood will be developed for the final package design.

Standard blister labeling includes trade name, active ingredient and strength, lot number, expiration date, company name, and bar code. Additionally, the individual blister cells need opening directions for the CR feature, a fragile statement, and the warning statement regarding addiction. The “habit-forming” statement is expected to be a requirement of the RMP and the purpose of the fragile statement is to minimize tablet damage by patients in the opening process. Labeling for the primary package will be proposed and discussed with the FDA at the pre-NDA meeting in April 2005. The proposed text fits on a 68X104 mm blister card in a perforated 2x2 configuration. While it is desirable to get agreement at the pre-NDA meeting, it is probable that the individual blister unit label will be negotiated as part of the RMP and labeling discussions with final copy at the time of NDA approval. Appendix 3 contains the material specifications for the blister card material and the label being proposed at the pre-NDA meeting.

The overall dimension and configuration of the final commercial blister card will be determined by the amount of real estate required for label copy on each blister cell. The dimensions impact package tooling equipment design and the purchase of that equipment is on the critical path for launch readiness. Technical Operations is evaluating contingency plans for a blister card larger than 68X104 mm card but no greater than 136 mm in length beyond which there is a significant impact to packaging line design and output. CR testing will be conducted on the final production equipment and blister configuration.

The proposal is for the commercial carton to contain 28 tablets. Labeling for the carton (secondary package) will also be proposed at the pre-NDA meeting. Specifications for the package insert and patient leaflet will be submitted with the NDA. It is expected that multiple patient leaflets will be required in each carton. That number will be determined by the titration schedule.

FEBT Drug Product Profile

Parameter	**Description**
Dosage strengths	100, 200, 400, 600, 800 mcg
Shape	**Round beveled-edge**
Colors	Dose — Color 100 mcg — White 200 mcg — White 400 mcg — Pink 600 mcg — Orange 800 mcg — Yellow
Tablet markings	Debossed with Cephalon "C" logo on 1 side and 1-digit strength-identifier code on other side (last digit of the NDC).
Trade Packages	Unit dose packaging (foil/foil) blisters 100 mcg — XX count — NDC 63459-541-XX 200 mcg — XX count — NDC 63459-542-XX 400 mcg — XX count — NDC 63459-544-XX 600 mcg — XX count — NDC 63459-546-XX 800 mcg — XX count — NDC 63459-548-XX
Sample Package	There are no sample packages for this product. Any sampling will use coupon/commercial product.

VIII. Market Development

FEBT provides Cephalon the opportunity to extend the pain franchise beyond the patent expiration of ACTIQ®. The novel dosage form has unique advantages which could translate to patient preference and possible faster therapeutic effect. Market development activities for FEBT are planned or already in process with the objective of launching FEBT for BTCP in 3Q '06, and for "relaunching" with an expanded label for BTP 1 year later. Because ACTIQ® is projected to lose patent protection in 3Q '06, it is vital that FEBT is ready for launch as soon as FDA approval is obtained.

The table below outlines the FEBT market development activities and time lines:

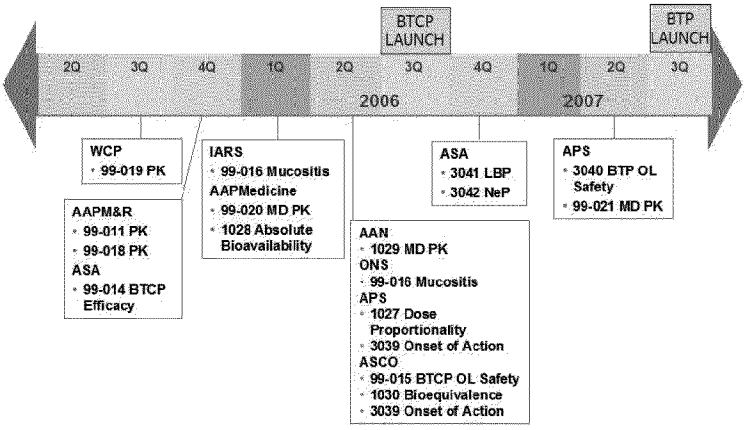
Activity	Description	Start Date	Completion Date
Trade name development	Vendor development of trade name options (final identification and registration by Cephalon TBD)	3Q '04	1Q '05
Package design	Identify the most cost-effective optimal package design that meets child-safety requirements, simplifies the titration process, convenient size and quantity to meet pharmacy/provider/patient needs	3Q '04	2Q '05
Communication plan development	Plan presents the communication strategy with regard to dissemination of key messages via publications, symposia, other media, and thought leader development	3Q '04	1Q '05 (Implementation of plan will be ongoing)
Preliminary marketing plan development	Comprehensive plan detailing initial product profile, key marketing issues, strategies, positioning, messaging, target audience, etc	4Q '04	1Q '05
Advertising agency selection	Selection of a strategic partner to effectively and efficiently prepare FEBT for commercialize	4Q '04	4Q '04
Creation and testing of branding elements	Creation of logo, color, and other branding elements	2Q '05	2Q '05
Development and testing of positioning	Creation of product position statement and its supporting messages	1Q '05	2Q '05
Thought leader development	Introduction FEBT to thought leaders, involve thought leaders in the clinical and commercial planning process	1Q '05	Ongoing
Managed care and third-party payers strategy	Determine contracting strategy to optimize FEBT reimbursement	3Q '05	3Q '06
Risk management program	Development of materials to meet RMP needs	1Q '06	3Q '06
Forecast refinement	Implementation of appropriate market research to refine FEBT forecast	4Q '04	Ongoing
Pricing	Identification of pricing strategy based on product attributes and projected market conditions via a pricing study	2Q '05	1Q '06
Market assessment	Ongoing tracking of the market and competitors	4Q '04	Ongoing

Activity	Description	Start Date	Completion Date
Campaign development	Creation, testing, and production of launch campaign materials	4Q '05	3Q '06
Sales force strategy	Identification of the optimal sales force size and alignment	1Q '05	Ongoing
Publication submission*	99-10 – PK		3Q '05
Publication submissions	99-011 – PK, 99-018 – PK, 99-014 – BTCP Efficacy		4Q '05
Publications submission	3039 – Onset of Action 99-016 – Mucositis 1027 – Dose Proportionality		2Q '06
Publications submission	99-015 – BTCP 0L Study 1028 – Absolute Bioavailability 1029 – MD PK		3Q '06
Publications submission	1030 – Bioequivalence 3041 – LBP		4Q '06
Publications submission	3042 – NeP		1Q '07
Publications submission	3040 – BTP OL Safety		3Q '07

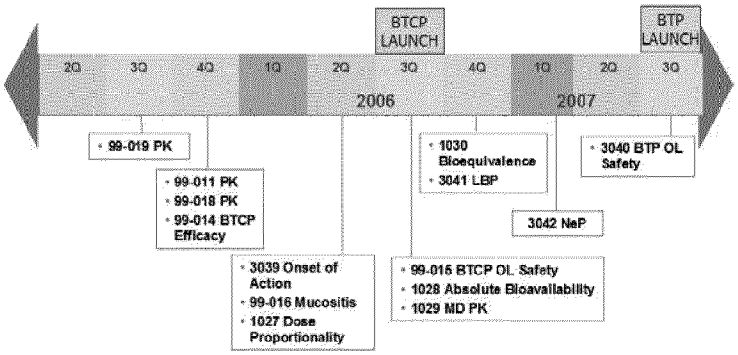
IX. Publications Strategy

The FEBT publications plan is designed to dovetail into the overall commercialization strategy and will capitalize on the Clinical Program. Its objectives and goals are to create a presence in the literature (both as congress abstracts and peer-reviewed journal articles) by communicating results of clinical research efforts, to communicate consistent messages across all submissions, and to establish potential advantages of FEBT in cancer and other forms of BTP. Messaging incorporated into the publications will be aligned with the desired claims. PK and clinical data will be rolled out as they become available, resulting in congress presentations and publications as the FEBT launch approaches. The illustrations below depict the time lines for presentations and publications developed out of the Clinical Program.

Congress Presentations Time Line



Publications Time Line

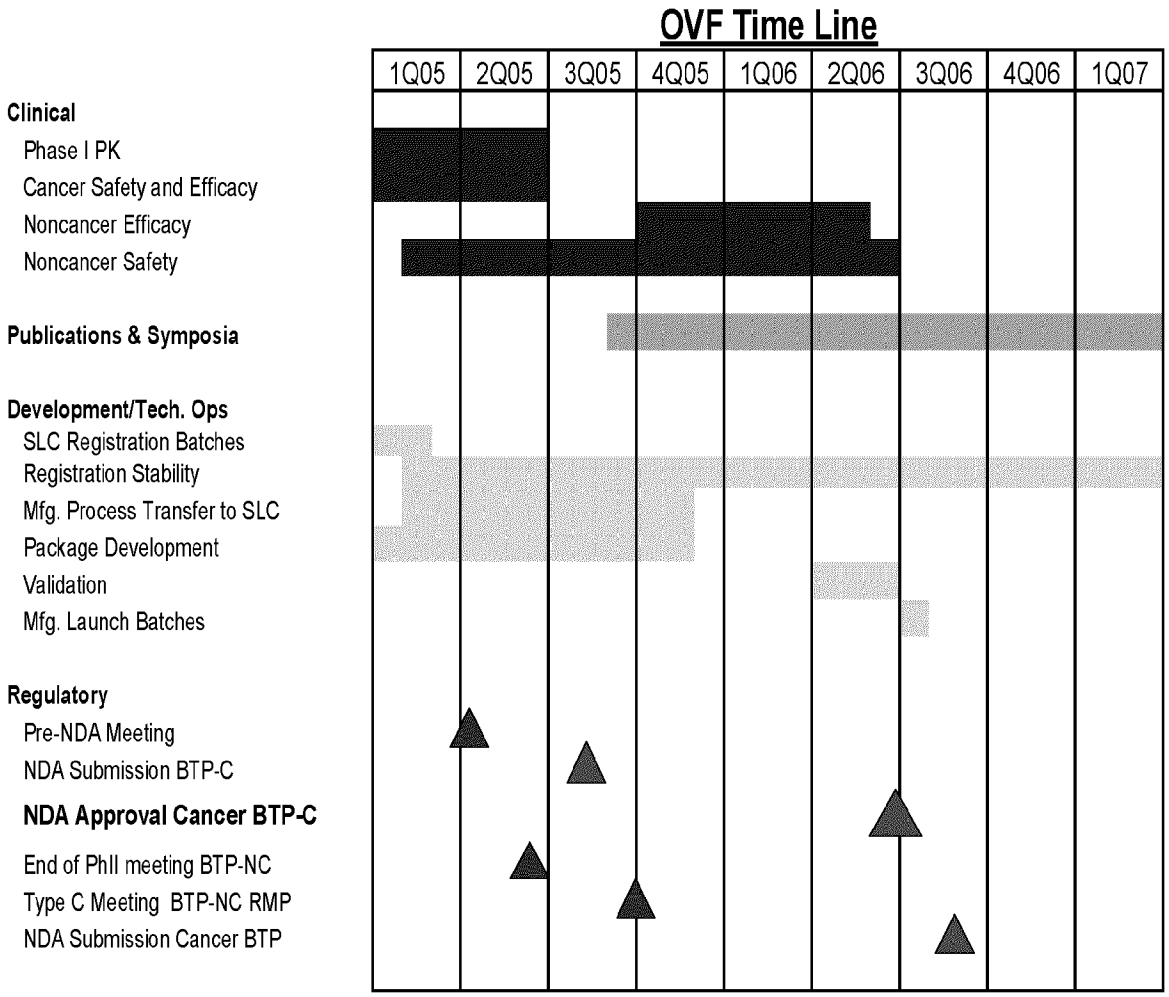


Because the expected target audience is composed of pain specialists and oncologists, congress choices are based on reaching these physicians as well as expected data availability. The target congresses for presentations in 2005 are the World Congress of Pain (WCP), American Academy of Physical Medicine & Rehabilitation (AAPM&R), and American Society of Anesthesiology (ASA). In 2006, the American Association of Pain Medicine (AAPM), International Anesthesia Research Society (IARS), American Academy of Neurology (AAN), American Pain Society (APS), Oncology Nursing Society (ONS), American Society of Clinical Oncology (ASCO), and the ASA will be targeted for submissions.

The journals targeted for manuscript submissions are primarily pain or oncology journals. Some of the PK study manuscripts will be directed towards pharmacology journals to broaden the audience receiving FEBT messages. Secondary/review articles intended to promote BTP

awareness are also planned for submission to further set the stage for the FEBT launch. In selecting appropriate journals, attention was given to journal scope, circulation, impact factor, submission to publication time, and acceptance rates. Consideration of these factors should allow timely publication of PK and clinical data in support of the FEBT launch.

X. Time Lines



Time line for NDA submission for indication in cancer BTP

Milestones	Target Start Date	Target Completion Date	Status
Pre IND Meeting	4Q '01	4Q '01	Complete
IND Filing	3Q '02	3Q '02	Complete
EOP 2 Meeting	4Q '03	4Q '03	Complete
Brooklyn Park Registration Batches	2Q '04	2Q '04	Complete
Initiate Brooklyn Park Stability	4Q '03	1Q '04	Complete
Eden Prairie Site Registration Batches	4Q '04	4Q '04	Complete
Pre-NDA Meeting	2Q '05	2Q '05	
Initial Efficacy Studies	2Q '04	4Q '04	Ongoing
SLC Registration Batches	4Q '04	1Q '05	Ongoing
Finalize Primary Package Specifications	3Q '04	2Q '05	Ongoing
NDA Submission	3Q '05	3Q '05	
Open-Label Safety Study	2Q '04	1Q '05	Ongoing
Onset of Action Study	1Q '05	1Q '05	Ongoing
Additional PK Studies	1Q '05	1Q '05	Ongoing
Additional Efficacy Trial – Onset	1Q '05	2Q '05	
Manufacture Validation Batches	2Q '06	2Q '06	
NDA Approval	3Q '06	3Q '06	
Launch	3Q '06	3/4Q '06	

sNDA Time line for submitting noncancer BTP

Milestones	Target Start Date	Target Completion Date	Comments
Pre-NDA Meeting	4Q '05	4Q '05	
sNDA Submission	3Q '06	3Q '06	
Open-Label Safety Study	1Q '05	1Q '06	
Efficacy Study – Low Back Pain	3Q '05	1Q '06	
Efficacy Study – Neuropathic Pain	3Q '05	1Q '06	
sNDA Approval	3Q '07	3Q '07	
Publication of Phase III Efficacy Data	1Q '07	1Q '07	

Appendix I

Draft Package Insert

DOSAGE AND ADMINISTRATION

FEBT is contraindicated in non–opioid-tolerant individuals.

FEBT should be individually titrated to a dose that provides adequate analgesia and minimizes side effects (see **Dose Titration**).

As with all opioids, the safety of patients using such products is dependent on healthcare professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

FEBT should be kept out of the reach of children. Patients should dispose of any tablets remaining from a prescription as soon as they are no longer needed. Unused tablets should be removed from their blister pouch and flushed down the toilet.

TABLET ACCESSING

Do not open the blister until ready to administer. For single tablet removal, separate one of the 4 blister units by tearing apart at the perforations. Bend the unit along the line where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

TABLET ADMINISTRATION

Using dry hands remove the tablet from the blister unit and immediately place the entire FEBT tablet between the upper cheek and gum. Patients should not attempt to split the tablet. The FEBT tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. The FEBT tablet should not be sucked or chewed. A tablet dose of FEBT, if chewed or swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.

The FEBT tablet normally dissolves within 15 minutes after placement. If after 30 minutes the FEBT tablet is not completely dissolved, it can be swallowed. If signs of excessive opioid effects appear before the tablet is completely dissolved, the tablet should be removed from the patient's mouth. Future doses may need to be decreased (see **Disposal of FEBT)**.

Patients and caregivers must be instructed that FEBT contains medicine in an amount that could be fatal to a child. Patients and caregivers should be advised to dispose of any tablets remaining from a prescription as soon as they are no longer needed (see **Disposal of FEBT**).

DOSE TITRATION

The initial dose of FEBT to treat episodes of BTCP should be 100 mcg. For patients already receiving ACTIQ, please see ***Conversion ACTIQ to FEBT****.*

From this initial dose, patients should be closely followed and the dosage level changed until the patient reaches a dose that provides adequate analgesia using a single *FEBT* dosage tablet per BTCP episode. Patients should record their use of *FEBT* over several episodes of breakthrough

cancer pain and review their experience with their physicians to determine if a dosage adjustment is warranted.

Increasing the Dosage Level: Increases in the dose should be made until the patient reaches a dose that provides adequate analgesia for an episode of BTCP. During this titration phase the doses used should match those of the available strengths of FEBT. Available dosage strengths of FEBT are 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg. Dosage strengths should not be skipped. Multiple tablets may be used to produce mcg equivalents to available doses (see **PHARMACOKINETICS**).

Each new dose of *FEBT* used in the titration period should be evaluated over several episodes of BTCP to determine whether it provides adequate efficacy with acceptable side effects. The incidence of side effects is likely to be greater during this initial titration period compared to later, after the effective dose is determined.

Redosing Within a Single BTCP Episode: Patients may repeat dosing during a single episode of BTCP. The second dose should be equal to the strength of the initial dose taken during a BTCP episode. Redosing may occur 30 minutes after the start of the initial dosing during a single BTCP episode.

Daily Limit: Once a successful dose has been found, if patients experience greater than 4 BTCP episodes per day, the dose of the long-acting opioid used for persistent cancer pain should be re-evaluated.

Conversion ACTIQ to FEBT

It is important to recognize that patients using other forms of transmucosal fentanyl for BTCP cannot be switched to the same doses of FEBT. The pharmacokinetic profiles of other forms of transmucosal fentanyl are different from FEBT. In adult patients previously receiving ACTIQ® (oral transmucosal fentanyl citrate) CII for BTCP, the initial episode dose of FEBT should be as shown in Table X:

Table X

Current ACTIQ dose (µg) per BTCP Episode	FEBT Initial Titration Dose (µg)
200	100
400	100
600	100
800	200
1200	400
1600	600

DOSAGE ADJUSTMENT

Experience in a long-term study of FEBT used in the treatment of BTCP suggests that dosage adjustment of both FEBT and the maintenance (around-the-clock) opioid analgesic may be required in some patients to continue to provide adequate relief of breakthrough cancer pain. Generally, the FEBT dose should be increased when patients require more than 1 dosage tablet per cancer BTP episode for several consecutive episodes.

DISCONTINUATION OF FEBT

For patients requiring discontinuation of opioids, a gradual downward titration is recommended because it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

Appendix II

Overview of Clinical Studies

Efficacy 099-14 Pivotal Efficacy – Ongoing

Purpose: To serve as the pivotal efficacy trial for FEBT in cancer patients with BTP.

Objectives: To evaluate the analgesic efficacy and safety of FEBT vs placebo through the following measures:

- SPID at 0 to 30 minutes
- PID at 15, 30, 45, and 60 minutes
- PR at 15, 30, 45, and 60 minutes
- TOTPAR at 0 to 30 minutes
- Global evaluation of analgesic efficacy
- Evaluate the safety of FEBT

Study Design: The study design is nearly identical to that employed with the pivotal studies conducted with ACTIQ®. Patients are started on the 100-mcg dose and titrated to a successful dose. Once a successful dose (one that effectively controls 2 consecutive episodes of BTP without unacceptable adverse events) is obtained, patients qualify for entry into the double-blind randomization phase. During this phase of the trial, patients will be randomized to receive a prespecified sequence of 10 blinded doses of study medication (7 FEBT and 3 placebos). After each dose, patients evaluate the analgesic efficacy of the treatment for 60 minutes. Rescue medication (oral immediate-release opioids) is permitted 30 minutes after the start of FEBT dosing. Patients completing the DB phase are permitted to enter the Open-Label Extension Study (099-15).

Population:

- N = 120 entered and 70 randomized
- Patients with cancer that have 1 to 4 BTP episodes per day
- On ≥60 mg/day of oral morphine or equivalent
- Currently receiving opioids for BTP
- Adverse events

Outcome Variables:

- Pain intensity
- Pain relief
- Global assessment of medication effectiveness
- Proportion of patients requiring rescue
- Time from study medication dose to next BTP episode

099-15 Cancer Open-Label 12-Month Safety – Ongoing

Purpose: To provide safety data on enough patients to meet the 500-patient exposure requirement set by the FDA at the End of Phase II meeting for FEBT.

Objectives:

- To evaluate the safety associated with longer-term (up to 12 months) use
- To evaluate the global analgesic effectiveness over time
- To evaluate the safety of switching ACTIQ®-treated patients to FEBT

Design: Open-label safety study lasting up to 12 months. Patients entering from the pivotal efficacy studies will continue into this trial on the successful dose previously established. This dose may be titrated up or down as required. For patients entering this study without previous exposure to FEBT, a titration paradigm similar to that conducted in the 099-14 Study will be performed. Those entering the trial on higher doses of ACTIQ® (800, 1200, or 1600) will begin administering the dose of FEBT at 1 dose below half the ACTIQ® dose (eg, subjects entering trial on 1200 mcg of ACTIQ® will begin dosing at 400 mcg). Visits in this study will occur monthly.

Patients:

- N ~400 entered (100 from the efficacy studies)
- Patients completing the 99-014 or 3039 studies or new patients meeting the same entrance criteria
- Patients with cancer that have 1 to 4 BTP episodes per day
- On >60 mg/day of oral morphine or equivalent

Outcome Variables:

- Safety
- Global evaluation of effectiveness
- Average dose at beginning and end of treatment
- Proportion of patients previously using ACTIQ® who achieve successful treatment with FEBT at half the ACTIQ® dose
- Proportion of patients who prefer FEBT over their previous BTP treatment
- Adverse events

Study C25608/3039/BP/US Pivotal Efficacy

Purpose: To serve as an additional pivotal trial that generates data which can be used to differentiate FEBT from ACTIQ® (assessment of analgesia at earlier time points and onset of meaningful pain relief) and provide data on switching patients from ACTIQ® to FEBT.

Objectives:

- To evaluate the efficacy of FEBT vs placebo through the following measures:
  - Time to meaningful pain relief (stopwatch)
  - PID at 5, 10, 15, 30, 45, 60, 90, and 120 minutes
  - SPID at 60 minutes and 120 minutes
  - PR at 5, 10, 15, 30, 45, 60, 90, and 120 minutes
  - TOTPAR 0-60
  - Global Evaluation
  - Patient Preference
  - Safety

Study Design:

The design of this study is nearly identical to that of the other efficacy trial, Study 099-14. After meeting entry criteria, patients will undergo an open-label titration with FEBT in order to identify a successful dose for each patient. The starting dose will be 100 mcg for most patients. Those entering the trial on higher doses of ACTIQ® (800, 1200, or 1600 mcg) will begin dosing at a dose of FEBT that is 1 dose level below half the ACTIQ® dose (ie, patients entering the trial on 1200 mcg of ACTIQ® will begin dosing with FEBT at 400 mcg). All patients will be titrated up until a successful dose of FEBT (one that effectively controls 2 consecutive episodes of BTP without unacceptable adverse events) is found. Those patients who find a successful dose between 100 and 800 mcg will qualify for entry into the double-blind period of the study.

During the double-blind period of the trial, patients will be randomized to receive a prespecified sequence of 10 doses of blinded study medication (3 placebos, 7 FEBT). They will be instructed to take the doses in a predetermined order for successive BTP episodes. Following each dose, patients will measure pain intensity, pain relief, identify when meaningful pain relief is achieved, and provide a global medication performance assessment.

Population:

- N = 100 entered and 70 randomized and evaluable
- Patients with cancer that have 1 to 4 BTP episodes per day
- On >60 mg/day of oral morphine or equivalent
- Currently receiving opioids for BTP

Outcome Variables:

- Pain intensity
- Time to meaningful pain relief
- Pain relief
- Global evaluation of efficacy
- Time from study medication dose until next episode of BTP
- Proportion of patients previously using ACTIQ® who achieve successful treatment with FEBT at 1 dose level less than one half the ACTIQ® dose
- Proportion of patients who prefer FEBT over their previous BTP treatment
- Adverse events

Study 1027 Dose Proportionality

Purpose: To determine if the PK profile of FEBT is linear across the dose range and to generate PK information on each strength of FEBT with the intent of having it described within the label as is done with ACTIQ®.

Objective: To determine the C_{max}, AUC, and t_{max} for each dose strength of FEBT (100, 200, 400, 800 mcg).

Design: Single-dose open label crossover

Population:

- N = 24
- Healthy volunteers

Outcome Variables:

- C_{max}, AUC, and t_{max}
- Plasma curves over a 6-hour period

Study 1026 Bioequivalence of four 100-mcg tablets to one 400-mcg tablet

Purpose: To establish the data necessary to allow patients to use multiple doses of 100 mcg to titrate to an effective dose, making the initial titration with FEBT more convenient.

Objective:

1. To determine if four 100-mcg tablets are bioequivalent to one 400-mcg tablet of FEBT
2. To determine PK profile of FEBT with arterial sampling

Design: Single-dose open-label crossover

Population:

- N = 24
- Healthy volunteers

Outcome Variables:

- C_{max}, AUC, and t_{max}

Study 1029 Multiple Dose PK

Purpose: To establish the steady state PK profile and determine if there is any dose accumulation

Objective: To establish the steady state PK profile of FEBT

Design: Single- and multidose open-label crossover

Population:

- N = 24
- Healthy volunteers

Outcome Variables:

- C_{maxss}, AUC_{ss}, and t_{maxss}

Study 1028 Absolute/Relative Bioavailability

Purpose: To determine the proportion of fentanyl absorbed via buccal mucosa compared to ACTIQ®

Objectives: a. To establish the absolute bioavailability of the FEBT dose

b. To determine the relative bioavailability of FEBT to ACTIQ® and swallowed Fentanyl

Design: Single-dose open-label crossover with equivalent doses of IV fentanyl, oral solution of fentanyl, FEBT, and ACTIQ®

Population:

- N = 24
- Healthy volunteers.

Outcome Variables

- C_{max}, AUC, and t_{max}.

099-16 Tolerability and PK in Patients With Mucositis

Purpose: To obtain data on the use of FEBT in cancer patients with mucositis

Objective:
a. To evaluate the tolerability of FEBT in patients with mucositis
b. To evaluate the PK profile of FEBT when administered to patients with mucositis

Design: Single-dose open-label study

Population:

> N = 12
> Cancer patients who are opioid-tolerant and have mucositis

Outcome Variables:

> Mucosal irritation
> AEs
> C_{max}, AUC, and t_{max}

Study 3041 Neuropathic Pain Efficacy

Purpose: To serve as a pivotal efficacy trial in the submission for an expanded indication into BTP in patients with chronic, noncancer pain

Objectives:

> To evaluate the analgesic efficacy of FEBT vs placebo as measured by
  - SPID 0 to 60 minutes
  - Time to meaningful pain relief
  - PID at 5, 10, 15, 30, 45, 60, 90, and 120 minutes
  - SPID at 60 and 120 minutes
  - PR at 5, 10, 15, 30, 45, 60, 90, and 120 minutes
  - Preference of FEBT compared to previous BTP medication
  - Safety

Design: The design of this study is nearly identical to that of the other efficacy trial, Study 099-14. After meeting entry criteria, patients will undergo an open-label titration with QVF in order to identify a successful dose for each patient. The starting dose will be 100 mcg for most patients. All patients will be titrated up until a successful dose of FEBT (one that effectively controls 2 consecutive episodes of BTP without unacceptable adverse events) is found. Those patients who find a successful dose between 100 and 800 mcg will qualify for entry into the double-blind period of the study.

During the double-blind period of the trial, subjects will be randomized to receive a prespecified sequence of 10 doses of blinded study medication (3 placebos, 7 FEBT). They will be instructed to take the doses in a predetermined order following successive BTP episodes. Following each dose, patients will measure pain intensity, pain relief, identify the time at which meaningful pain relief is achieved, and provide a global medication performance assessment.

Population:

- Chronic neuropathic pain of at least a 3-month duration from postherpetic neuralgia, diabetic peripheral neuropathy, chronic regional pain syndrome, and traumatic injury
- On >60 mg/day of oral morphine or equivalent
- Experience 1 to 4 episodes of BTP per day
- Currently taking oral opioids for BTP

Outcome Variables:

- Pain intensity
- Time to meaningful pain relief
- Pain relief
- Global evaluation of efficacy
- Time from study medication dose until next episode of BTP
- Proportion of patients previously using ACTIQ® who achieve successful treatment with FEBT at 1 dose level less than 1 half the ACTIQ® dose
- Proportion of patients who prefer FEBT over their previous BTP treatment
- Adverse events

Study 3042 Low Back Pain Efficacy

Purpose: To serve as a pivotal efficacy trial in the submission for an expanded indication into BTP in patients with chronic, noncancer pain

Objectives:

- To evaluate the analgesic efficacy and safety of FEBT vs placebo as measured by:
  - SPID 0 to 60 minutes
  - Time to meaningful pain relief
  - PID at 5, 10, 15, 30, 45, 60, 90, and 120 minutes
  - SPID at 60 and 120 minutes
  - PR at 5, 10, 15, 30, 45, 60, 90, and 120 minutes
  - Preference of FEBT compared to previous BTP medication
  - Global assessment of medication performance
  - Safety

Design: The design of this study is nearly identical to that of the other efficacy trial, Study 099-14. After meeting entry criteria, patients will undergo an open-label titration with FEBT in order to identify a successful dose for each patient. The starting dose will be 100 mcg for most patients. All patients will be titrated up until a successful dose of FEBT (one that effectively controls 2 consecutive episodes of BTP without unacceptable adverse events) is found. Those patients who find a successful dose between 100 and 800 mcg will qualify for entry into the double-blind period of the study.

During the double-blind period of the trial, subjects will be randomized to receive a prespecified sequence of 10 doses of blinded study medication (3 placebos, 7 FEBT). They will be instructed to take the doses in a predetermined order following successive BTP episodes. Following each dose, patients will measure pain intensity, pain relief, identify the time at which meaningful pain relief is achieved, and provide a global medication performance assessment.

Population:

> Chronic low back pain of at least 3 months' duration from osteoarthritis, degenerative disc disease, or spondilolysthesis with supportive radiographic evidence and a functional disability
> On >60 mg/day of oral morphine or equivalent
> Experience 1-4 episodes of BTP per day
> Average episode lasts 4 hours or less
> Currently taking oral opioids for BTP

Outcome Variables:

- Pain intensity
- Time to meaningful pain relief
- Pain relief
- Global evaluation of efficacy
- Time from study medication dose until next episode of BTP
- Proportion of patients previously using ACTIQ® who achieve successful treatment with FEBT at 1 dose level less than half the ACTIQ® dose
- Proportion of patients who prefer FEBT over their previous BTP treatment
- Adverse events

Study 3040 Noncancer Open Label 12-Month Safety

Purpose: To enroll enough patients to achieve a total of 300 patients treated for 6 months and 100 patients treated for 1 year

Objectives:

> To evaluate the safety associated with longer-term (up to 12 months) use
> Evaluate the global analgesic effectiveness over time
> Evaluate the impact of FEBT on patient-reported outcomes

Design: Open-label safety study lasting up to 12 months. Patients entering from the pivotal efficacy studies in noncancer pain (3041 and 3042) will continue into this trial on the successful dose previously established. This dose may be titrated up or down as required. For patients entering this study without previous exposure to FEBT, a titration paradigm similar to that conducted in the pivotal efficacy trials will be performed. Visits in this study will occur monthly.

Patients:

> N ~750 entered (100 from the efficacy studies)
> Patients completing the pivotal studies
> Patients with chronic noncancer pain that have at 1 to 4 BTP episodes per day
> Average episode of BTP is 4 hours or less
> On >60 mg/day of oral morphine or equivalent

Outcome Variables:

> Safety
> Global evaluation of effectiveness

- Average dose at beginning and end of treatment
- Function scale (modified Oswestry, goal-attainment scale)
- Patient preference for BTP medication
- Brief Pain Inventory Short Form
- Profile of Mood States
- SF-36

Appendix III

Primary Package Specifications and Proposed Primary Label

Primary Packaging Materials

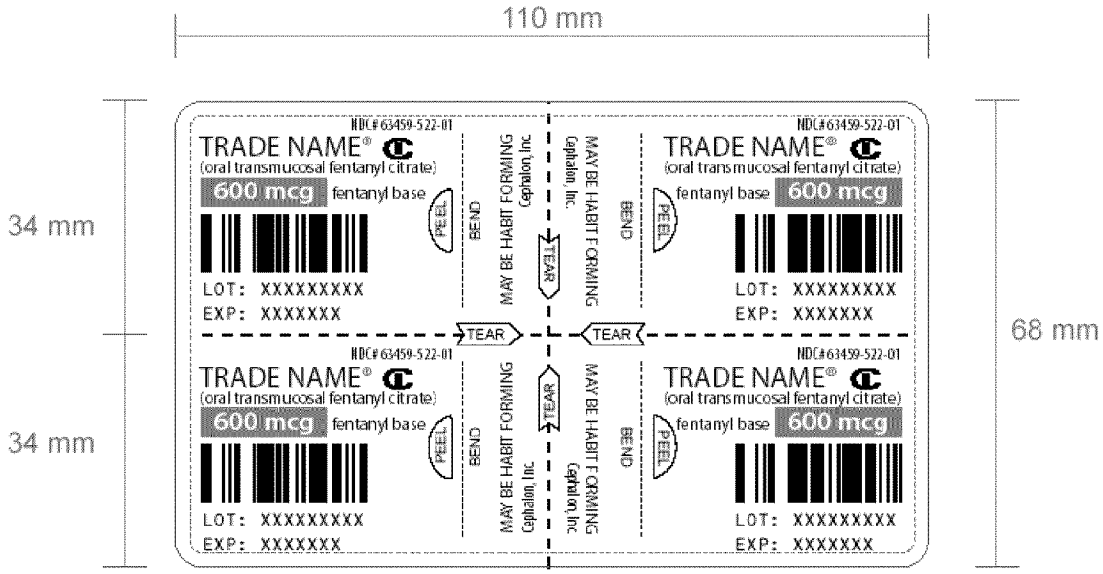
Bottom web: (Alcan 92011 and N FP036)	
PVC Film (60 micron)	Outside
adhesive	
Polyamide Film (25 micron)	
adhesive, ink, primer	
Aluminum Foil (60 micron)	
adhesive	
PVC Film (60 micron)	Inside, product contact

Lidding Material: CR peel = Alcan 15127

Paper (30#)	**Outside**
adhesive	
Polyester Film (12 micron)	
adhesive	
Aluminum Foil (25 micron)	

Proposed Blister Card Label

Lid Stock



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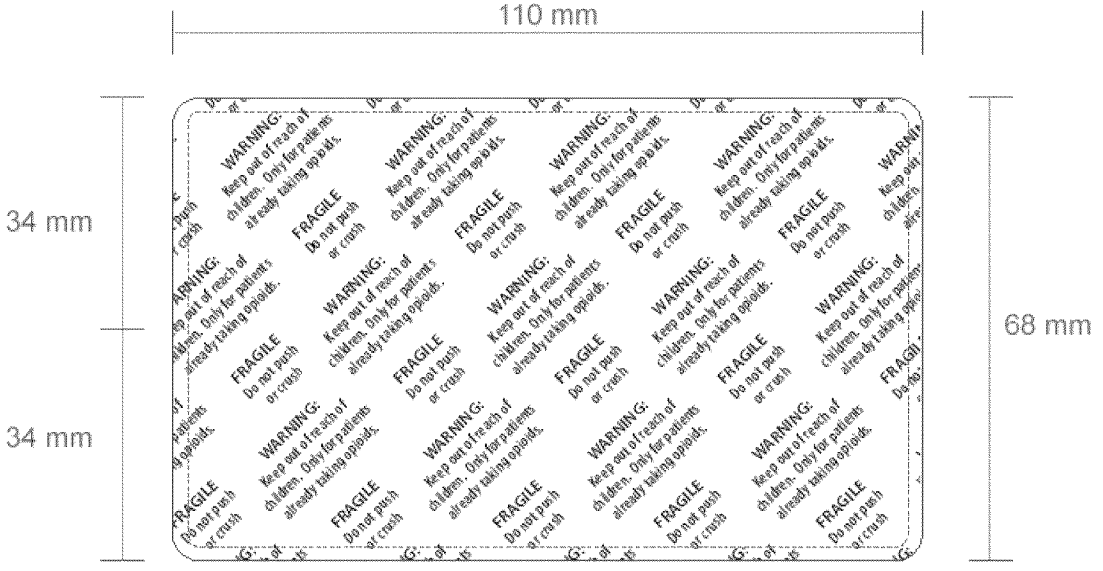
Dome Side



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Appendix IV

Glossary of Acronyms

API	active pharmaceutical ingredient
AUC	area under the drug concentration by time curve
BIO Eqi	bioequivalence
BST	Business Strategy Team
BTP-C	Break Through Pain in Cancer Patients
BTP-NC	Break Through Pain in Non Cancer Patients
C_{max}	peak plasma concentration
CR	child resistant
CRO	Contract Research Organization
CSR	clinical study report
FDA	Food & Drug Administration
FPFV	first patient first visit
HECON	Health economics
HEOR	Health economics and outcomes research
ICH	International Conference on Harmonization
IND	investigational new drug
LBP	low back pain
LPLV	last patient last visit
MD PK	multidose pharmacokinetics
NDA	new drug application
NPP	neuropathic pain
OL	Open Label

FEBT	OraVescent® Fentanyl
PBO	placebo
PCA	patient-controlled analgesia
PID	pain intensity difference
PK	pharmacokinetics
PR	Pain relief
P&RE	Pricing and reimbursement
RE	Reimbursement
RMP	Risk Management Program
SLC	Salt Lake City
sNDA	supplemental new drug application
SPID	sum of pain intensity difference
Ss	Steady state
t_{max}	time to reach peak plasma concentration

Appendix 4 Risk MAP

Background

Rationale for the RiskMAP

Fentanyl citrate has been marketed in the United States for more than 30 years, and the drug has a long record of safe and effective use when utilized as directed in the treatment of pain. Presently, fentanyl is marketed in the U.S. in a variety of formulations including those for intravenous or intramuscular administration as well as those intended for transdermal or oral transmucosal delivery.

TRADE NAME (fentanyl effervescent buccal tablets), a potent rapid-onset opioid analgesic with effects similar to morphine, has been evaluated in clinical trials at strengths of 100, 200, 400, 600, and 800 mcg for the treatment of breakthrough pain in patients with cancer who are tolerant to opioid therapy. Currently the only other drug marketed for the management of breakthrough pain in patients with cancer is ACTIQ®, a formulation of fentanyl citrate which is a lozenge dosage form on a handle. Like ACTIQ, TRADE NAME will be listed under the Controlled Substances Act as a CII product and labeling for the product will contain a boxed warning.

As noted by Food and Drug Administration (FDA) in its RiskMAP Guidance (2005), opiate drug products have important benefits in alleviating pain but are associated with significant risks of overdose, abuse, and addiction. FDA recommends that sponsors of Schedule II controlled substances consider developing RiskMAPs for these products. Because TRADE NAME contains a potent opiate, fentanyl, this RiskMAP is focused on minimizing three risks:

(1) Use of TRADE NAME by opioid non-tolerant individuals;

(2) Misuse, abuse and diversion of TRADE NAME; and;

(3) Unintended (accidental) exposure to TRADE NAME.

For each of these risks, a series of goals and accompanying measurable objectives have been established. In the implementation of the RiskMAP, tools will be employed to mitigate each of the risks. The overarching goal of this RiskMAP is to minimize specific risks associated with TRADE NAME while preserving the product's benefits.

Risks to be Minimized

Risk 1: Use of TRADE NAME by opioid non-tolerant individuals

As is the case with the use of all opioids, individuals using fentanyl citrate who are not tolerant to opioids are at risk for clinically significant and life-threatening adverse events such as respiratory depression. The risk is present at any dose in such individuals and the risk increases with dose. Therefore, TRADE NAME must not be used by opioid non-tolerant individuals as the safety and effectiveness of TRADE NAME in this population has not been established. Patients considered opioid-tolerant are those who are taking at least 60 mg of oral morphine per day, 25 mcg of transdermal fentanyl per hour, at least 30 mg of oxycodone daily, at least 8 mg oral hydromorphone daily, or an

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equianalgesic dose of another opioid for a week or longer. By limiting the use of TRADE NAME to those already taking opioid products for a sufficient time frame at sufficient levels, the risk of serious outcomes such as respiratory depression may be minimized.

TRADE NAME will likely be used primarily in the outpatient setting. To assure that at-risk patients are identified and that TRADE NAME is used only in opioid tolerant patients, Cephalon is initiating a risk-minimization program that contains multiple channels of communication and mutually reinforcing educational messages targeted toward physicians who prescribe TRADE NAME, pharmacists who dispense TRADE NAME, as well as toward the patients themselves.

Risk 2: Misuse, abuse and diversion of TRADE NAME

The abuse liability of opioids is well known and has been characterized in the medical and lay literature as well as in the media. Opioid misuse and abuse have been known to be a precursor to addiction. The actual rate of addiction to opioids is not known, but has been estimated to be between 4-10% (Savage 1996).

TRADE NAME is an effective opioid analgesic that delivers pharmacologically significant amounts of fentanyl to the brain. Fentanyl is a known drug of abuse, and the TRADE NAME dosage form (effervescent buccal tablets) has the potential to be abused. Consequently, TRADE NAME will be labeled, regulated, and listed as a Schedule II opioid, as are all other fentanyl products.

The pharmacokinetic and pharmacodynamic profile of a drug can influence its abuse liability. These are not fixed characteristics of the drug itself, but are affected by the dosage form and route by which the drug is delivered. The pharmacokinetic time course of effervescent buccal tablets is slower with lower peaks than comparable doses of injected fentanyl, and this suggests a reduced abuse liability for buccally administered TRADE NAME.

The abuse liability of a product is based on a complex interplay of many factors which include drug characteristics, patient characteristics, as well as societal and other influences. Among these many factors, rapid onset of action is a drug characteristic that may contribute to increased abuse liability. This view is supported by the evidence of attempts to reconstitute long-acting opioids into formulations with a rapid onset of action (eg, crushing Oxycontin tablets, withdrawing fentanyl from a patch for use in a syringe).

Though cases of abuse have been reported for ACTIQ, a product with a relatively fast onset of action, widespread abuse has not been identified.

Opioids, such as Oxycontin, have experienced 'geographic hot spots' and regional differences in abuse rates, where there is significantly more abuse or misuse and/or diversion than in most other geographic areas. Exact rates of diversion are not known, but diversion is known to have occurred as a result of pharmacy theft/loss, fraudulent prescriptions, individuals obtaining the medication from physicians under false pretenses, patients selling or otherwise diverting drugs, wholesaler loss, manufacturer loss, leftover product not being destroyed, and other factors.

In designing this RiskMAP, Cephalon has focused on ensuring the integrity of its supply chain for TRADE NAME, has identified tools that can be used to educate broadly, and is attempting to identify mechanisms by which cases of diversion or abuse as well as geographic incidents can be detected promptly.

Risk 3: Unintended (accidental) exposure to TRADE NAME

The risk of serious consequences from accidental exposure to TRADE NAME is greater in individuals not-tolerant to opioids. Therefore, the risk of unintended exposure to the drug can be viewed as a component of the first risk described above (use of TRADE NAME by opioid non-tolerant individuals). And while the tablet formulation and packaging of TRADE NAME is not expected to be intrinsically more interesting or appealing to children than tablet formulations in blister packs of other drugs, the epidemiology of accidental ingestions (which as described below occur primarily in the pediatric age group) and the risk of serious consequences from accidental exposure to TRADE NAME make the risk of unintended exposure to the product one that should be addressed in this RiskMAP.

Epidemiology of Unintended Poisonings

The literature on unintended poisonings in the United States indicates that children are at highest risk for accidental ingestion. Of 2.4 million poisonings reported to American Association of Poison Control Centers-Toxic Exposure Surveillance System (AAPCC-TESS) in calendar year 2003, 52% occurred in children aged less than 6 years. Epidemiologic data indicate that the peak incidence of accidental child poisoning is at 15 - 17 months of age, declining rapidly between ages 3 years through 6 years. This observed peak in poisoning incidence coincides with the period of increasing mobility of toddlers and resulting exploration of the environment that is commonly associated with oral exploratory (hand-to-mouth) behavior.

More than half of poison center contacts are due to the exposure of toxic substances to children less than 6 years of age. This same population comprises 3.1% of fatalities (AAPCC-TESS, 2003). This observation suggests that even though childhood exposures are common, the substances most commonly ingested by young children (eg, cosmetics, household cleaners, and plants) are usually of relatively low inherent toxicity. Similarly, fatalities as a result of pharmaceutical ingestions are observed in a similar manner, ie, in calendar year 2003, a total of 20 fatal pharmaceutical ingestions in children aged less than 6 years occurred; four fatal pharmaceutical ingestions in children aged 6 years - 12 years were reported.

There is considerable literature on the prevention of childhood poisoning. It has been documented that a substantial proportion of childhood poisonings can be prevented by keeping medications in child-resistant containers. In contrast, poison warning labels designed for children do not appear to be effective. Additionally, the ability of aversive bittering agents has not been proven to reduce the incidence or severity of childhood poisoning.

Implications of Poisoning Epidemiology for TRADE NAME

The efficacy and safety of TRADE NAME dosage strengths have been studied in the treatment of breakthrough pain only in adult opioid-tolerant patients. To date there are no data regarding the safety or efficacy of TRADE NAME in children. Given the known pharmacology of TRADE NAME, its rapid onset of action, and the dosage strengths available (up to 800 mcg of fentanyl), it can be anticipated that if a child who is not tolerant to opioids inadvertently is exposed to TRADE NAME, even in single unit doses, ingestion could result in significant toxicity or death.

Based on the epidemiological data cited above, it appears that the risk of accidental childhood poisoning involving TRADE NAME can be reduced through a number of mechanisms including child-resistant packaging and safety reminders (including instructions for proper storage, use, and disposal of medications), which remain the mainstay of poisoning prevention in young children. Cephalon will be using F1 packaging for TRADE NAME, which is the most stringent of child-resistant packaging requirements (see Glossary).

In addition, physicians who prescribe TRADE NAME can assess whether children are ever in the home of a patient. Directed counseling of these patients and those with children can be initiated and reinforced by healthcare professionals, including physicians, pharmacists and nurses, involved in the patient's care. These healthcare professionals can reinforce with the patient the need to prevent children's access to TRADE NAME. Patients themselves can be educated on the risk that TRADE NAME poses to children and can be given guidance on storage and disposal of the medication.

Although adults are less likely to experience unintended exposure to TRADE NAME than children, this RiskMAP also considered accidental exposure that could occur in adults, such as a result of cognitive impairment or due to medication errors. Steps could be taken to minimize such risks as well. For example, when prescribing TRADE NAME, physicians can assess the ability of their patients to self-administer the medication as directed. When this ability is in question, the patient's caregivers can be counseled by healthcare professionals with guidance similar to that given above to those with children in the home. Product distinctions in packaging, labeling, and the physical appearance of TRADE NAME are all factors that can contribute to decreasing the risk of medication errors which could be caused by inadvertent substitution of another medication for TRADE NAME.

In conclusion, as part of this RiskMAP, Cephalon is implementing interventions beyond product labeling specifically to target unintended TRADE NAME exposures (see section 0).

Risk-Benefit

Potential Benefits

Breakthrough pain (BTP) in patients with cancer is a well-recognized entity, and it is important that the pain be managed adequately as part of an overall pain management program for a patient. Because of the prevalence and inherent consequences of BTP, it is recommended that patients with chronic pain on regular opioid treatment regimen be

provided with supplemental opioid medications for the management of BTP (American Pain Society, 2003). For patients taking around-the-clock opioid therapy, the most commonly used medications for BTP are immediate-release oral opioids. It has been noted, however, that these medications are likely to be inadequate for a substantial proportion of patients (Portenoy et al 1999) because these medications typically take about 30 minutes to begin producing analgesic effects, whereas the onset of peak pain intensity of BTP for most patients occurs within just a few minutes.

As was shown in the pivotal randomized, double-blind, placebo-controlled efficacy study of cancer patients with breakthrough pain, TRADE NAME results in rapid onset of analgesia with extensive absorption and a lasting, even improving effect. The efficacy results showed that effervescent fentanyl had analgesic effects 15 minutes after tablet placement (the earliest time point assessed) and maintained superiority in analgesic effect compared with placebo treatment through the 60-minute observation period as evidenced by changes in pain intensity and pain relief scores. In addition, patients were twice as likely to require supplemental opioid analgesics for BTP episodes for which placebo was used than for those episodes for which effervescent fentanyl was used. The superiority of effervescent fentanyl to placebo treatment was demonstrated by all measures of efficacy (pain intensity, pain relief, global medication performance, and use of supplemental rescue medication) and at all time points (15, 30, 45, and 60 minutes after treatment). The effects were both statistically significant and clinically relevant.

While fentanyl has long been recognized as a potent analgesic, there are inherent advantages to the buccal tablet formulation of effervescent fentanyl. Fentanyl effervescent buccal tablets are uniquely formulated with effervescence ingredients and pH adjusters to facilitate a rapid and extensive absorption of fentanyl through the oral mucosa. Its observed pharmacokinetic profile indicates that approximately 50% of effervescent fentanyl is rapidly absorbed and quickly becomes systemically available. These formulation and pharmacokinetic characteristics mean that lower doses are needed by patients for attainment of therapeutically effective plasma concentrations than those required with ACTIQ, a fentanyl lozenge on a handle (solid dosage form). Specifically, this rapid absorption results in peak plasma concentrations being reached nearly twice as fast as ACTIQ, allowing for therapeutically effective plasma concentrations to be achieved earlier. These product qualities are advantageous for a condition such as BTP when the time from onset to maximum intensity is short. Because the effervescent formulation is a more efficient delivery system, the tablet strengths of effervescent fentanyl (100 to 800 mcg) are lower than the unit strengths of ACTIQ (200 to 1600 mcg).

Unlike administration of ACTIQ, a transmucosal fentanyl lozenge on a handle, administration of a buccal tablet is not only less patient dependent but is also more discreet and convenient for the patient. The simplicity of administration of a tablet potentially allows for more consistent delivery of fentanyl because it is less patient dependent (ie, a passive delivery system is less prone to patient error than an active delivery system).

Potential Risks

While TRADE NAME has been shown to benefit opioid-tolerant patients with breakthrough cancer pain, the product also has side effects and risks.

Because effervescent fentanyl is a potent opioid analgesic, it may produce side effects similar to those seen with other products of its class. In addition, the transmucosal route of delivery for effervescent fentanyl could lead to risk of oral mucosal irritation. On the basis of experience from clinical studies, about 8% of patients treated with effervescent fentanyl had adverse event that could be considered related to tablet application site (eg, application site pain, ulcer, or burning). In general, these adverse events were not serious and did not lead to stopping treatment. Additionally, opioid analgesics may impair mental and/or physical ability required for the performance of potentially dangerous tasks such as driving a car or operating machinery

As described above, because it is a potent μ-receptor agonist, there are inherent risks with effervescent fentanyl to populations for which the product is not intended, particularly people who are not opioid tolerant. One such risk is that of respiratory depression, although this side effect was not seen in clinical studies with effervescent fentanyl.

Like other drugs of its class, effervescent fentanyl may be habit forming or potentially abused, and as such, physicians should use caution when prescribing it to patients. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (eg, major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed effervescent fentanyl. All patients receiving effervescent fentanyl should be routinely monitored for signs of misuse, abuse, and addiction.

During clinical studies of effervescent fentanyl, there were no reports of patients abusing effervescent fentanyl or patients who experienced an overdose. Two patients in study 15 were withdrawn from the study at the request of the sponsor due to the theft of tablets of effervescent fentanyl from these patients' homes. In both cases, the patients had family members with a history of drug abuse, and there were questions about whether the family members were involved in the theft.

As with other fentanyl formulations (the transdermal patch or ACTIQ), the potential exists for abusers to extract fentanyl from effervescent fentanyl tablets. The efficiency of the effervescent delivery system enables similar plasma levels of fentanyl to be obtained with doses of fentanyl that are lower than those required with ACTIQ. The tablet strengths for effervescent fentanyl (100, 200, 400, 600, and 800 mcg) are half those of the available dose strengths for ACTIQ (200, 400, 600, 800, 1200, and 1600 mcg). Moreover, the amount of fentanyl in the effervescent tablets is also substantially lower than the 10 mg of fentanyl present in the 100-mcg/h transdermal patch. Although the risk of extraction is present for effervescent fentanyl, the amount of drug available is lower than with these other formulations.

Manipulation (eg, crushing) of the effervescent fentanyl tablets is not likely to substantially alter the absorption characteristics of the medication when administered buccaly or orally. Although intranasal and intravenous administration of a crushed tablet is possible, the risk of occurrence is not considered to be any greater than for other strong μ-opioids (eg, oxycodone, hydromorphone, or morphine).

There is also a risk of unintended exposure to TRADE NAME. The tablet formulation of TRADE NAME and its packaging is not expected to be intrinsically more interesting or appealing to children than tablet formulations and packaging of other drugs. But the epidemiology of accidental ingestions indicate that they occur primarily in the pediatric age group, and there is a risk of serious or fatal-consequences from accidental exposure to TRADE NAME, particularly in individuals not opioid tolerant.

Cephalon has developed a RiskMAP to mitigate three of the risks identified above: (a) use by opioid non-tolerant individuals; (b) misuse, abuse, and diversion; and (c) unintended (accidental) exposure to the medication.

The overall goal of this RiskMAP is to minimize the risks of TRADE NAME while preserving its important medical benefits.

RiskMAP Goals and Objectives

For purposes of this RiskMAP, Cephalon uses the term "goals" and "objectives" in a manner consistent with FDA's Guidance for Industry: Development and Use of Risk Minimization Action Plans (2005). These definitions emphasize that whereas goals are absolute and ideal, objectives are pragmatic and measurable (Section III.C of the guidance):

> *FDA suggests that sponsors state goals in a way that aims to achieve maximum risk reduction. The following are examples of RiskMAP goals: "patients on X drug should not also be prescribed Y drug" or "fetal exposures to Z drug should not occur." FDA recommends that goals be stated in absolute terms. Although it might not be possible to ensure that absolutely no one on X drug receives Y drug, FDA believes that a goal as the term implies is a statement of the ideal outcome of the RiskMAP.*
>
> *FDA recommends that RiskMAP goals be translated into pragmatic, specific and measurable program objectives that result in processes or behaviors leading to achievement of the RiskMAP goals Objectives can be thought of as intermediate steps to achieving the overall RiskMAP goal. A RiskMAP goal can be translated into different objectives, depending upon the frequency, type, and severity of the specific risk or risks being minimized. For example, a goal may be the elimination of dangerous concomitant prescribing. The objectives could include lowering physician co-prescribing rates and/or pharmacist co-dispensing rates.*

Cephalon has identified three goals that express the ideal outcome of the TRADE NAME RiskMAP. These goals are based on the risks identified in section 0 (Risks to be Minimized). With each of these goals, there are specific and measurable program objectives that are described below.

Goals

(1) Goal 1: TRADE NAME should be used only by opioid tolerant individuals.
(2) Goal 2: Abuse, Misuse and Diversion of TRADE NAME should not occur.
(3) Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur.

Objectives

Goal 1: TRADE NAME should be used only by opioid tolerant individuals

Objectives:

i. To educate practitioners that TRADE NAME should not be used in opioid non-tolerant patients
ii. To ensure patients understand that TRADE NAME should be used only by individuals who are opioid tolerant

iii. To educate prescribers and other healthcare personnel (eg, pharmacists and nurses) so that they are aware of the importance of TRADE NAME being prescribed, distributed, and administered only to opioid tolerant patients.

Goal 2: Abuse, Misuse and Diversion of TRADE NAME should not occur

Objectives:

i. To ensure adequate controls are instituted, evaluated, and maintained to prevent the diversion of TRADE NAME from Cephalon's supply chain.

ii. To ensure adequate education, surveillance, and interventions are instituted and maintained to minimize diversion of TRADE NAME when the product is no longer within Cephalon's supply chain.

iii. To reduce the potential abuse, misuse, and diversion of TRADE NAME by (a) providing education to healthcare personnel and to pertinent nationwide demographic communities; (b) performing ongoing surveillance of abuse, misuse, and diversion; and, (c) cooperating with and providing assistance to law enforcement in investigations of incidents of abuse or diversion.

Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur

Objectives:

i. To reduce or eliminate accidental exposure through product packaging which has been designed and tested so as to reduce or eliminate unintended access to TRADE NAME by at-risk populations.

ii. To reduce or eliminate accidental exposure by properly educating patients about "safe product use" at the point of prescribing and dispensing.

iii. To reduce or eliminate departures from "safe product use" at the time of actual or intended use of TRADE NAME.

iv. To reduce or eliminate accidental exposure during storage of TRADE NAME and to ensure that mechanisms exist to facilitate the prompt return and/or disposal of all unused TRADE NAME when it is no longer needed.

Strategy and Tools

Overall Strategy

Cephalon developed the RiskMAP for TRADE NAME with specific reference to FDA and International Conference on Harmonisation (ICH) Guidances entitled *"Guidance for Industry: Development and Use of Risk Minimization Action Plans"* and *"Quality Risk Management Q9."* In the development of the RiskMAP, Cephalon also called on its extensive knowledge and experience with implementing its Risk Management Program for ACTIQ, a closely related product. In addition, principles and methodology of other risk assessment tools, such as Failure Mode Effects Analysis (FMEA), were used to evaluate the potential risks associated with use of TRADE NAME.

Failure Mode Effects Analysis (FMEA) is a systematic, prospective risk-analysis process. Prospective risk management activities allow pharmaceutical companies to minimize the occurrence of errors, whereas a retrospective activity, such as root-cause analysis, analyzes errors after they have occurred. An objective of Cephalon's application of some of the principles and methodology of FMEA is to minimize the occurrence of the identified risks by scrutinizing the identified system processes. FMEA employs the following six steps:

(1) Choose a process for investigation.
(2) Form a multidisciplinary team.
(3) Map out the process, including each step.
(4) Calculate a risk priority for each step in the process.
(5) Select an area for improvement based on the calculated risk priority.
(6) Implement actions and outcome measures.

A multidisciplinary team was assembled, which was comprised of representatives with expertise from several different areas, including medical, legal, regulatory, commercial, and scientific affairs, with the purpose of identifying anticipated risks that could occur with the commercialization of TRADE NAME. The team identified 3 principal risks which have been described above (see section 0: Risks to be Minimized). The team then analyzed the points of intervention where undesirable incidents could occur, beginning with the initial steps in commercialization of the product and ending with the disposal of the product. The six points of intervention identified were the following:

(1) supply chain;
(2) point of prescribing;
(3) point of dispensing;
(4) consumer storage;
(5) patient use (also referred to as consumer use); and,
(6) disposal of product.

The team then considered tools that are currently available, those which are familiar to Cephalon through its ACTIQ Risk Management Program, and those identified through

consultation with outside experts. Subsequently, each risk was assessed to determine the potential success of the tools at each of the 6 points of intervention. The points where potential failures could occur were than identified and tools were selected to minimize the risks at these points. Appendix A summarizes principal tools being employed in this RiskMAP.

Following a reasonable time after commercialization of TRADE NAME, such as when sufficient data have been accumulated to ascertain whether the key messages are being adequately communicated (eg, approximately 6-12 months), the risks associated with TRADE NAME and points of departure from the principles of the RiskMAP will be analyzed, if possible using some of the principles of FMEA. When feasible, these analyses will review each type of risk for seriousness or severity and will provide an estimate of frequency or probability of the event. An example of how a criticality index can be estimated in such an analysis is described in Table 1.

Table 1: An Example of the Application of the Criticality Index in Failure Mode and Effects Analysis

Rating	Potential Effect of Risk on Patient (Seriousness or Severity)	Frequency of Error	Likelihood of Error Reaching Patient
10	Catastrophic	Frequent	Absolute
7-9	Major	Occasional	Probable
4-6	Moderate	Uncommon	Possible
1-3	Minor	Remote	Doubtful

In formal quantitative FMEA, a criticality index can be calculated by multiplying the mean rating scores for severity/seriousness, frequency of error, and likelihood of reaching the patient. Higher scores of the criticality index represent more critical errors and can help identify the most important failures in a system and identify areas where key messages might need to be reinforced or where interventions might need to be adjusted.

Several key messages will be provided to health professionals and patients in the redundant tools throughout the RiskMAP. They will convey that TRADE NAME:

- contains fentanyl citrate,
- is a Schedule II opioid,
- should be used by opioid-tolerant patients (defined by the package insert) because of the risk of serious outcomes such as respiratory depression
- has a risk of misuse, abuse, and diversion
- should be kept out of the reach of children,
- is indicated for breakthrough pain in patients with cancer, and

- is contraindicated in acute pain or post-operative pain.

A principal goal of the RiskMAP is to ensure that physicians, pharmacists, and patients are aware and knowledgeable of each of these messages and their implications.

Strategy and Tools Associated with Goal 1: TRADE NAME should be used only by opioid-tolerant individuals

A variety of tools will be used to communicate and reinforce the message that TRADE NAME should be used only by opioid-tolerant individuals. The tools selected have been chosen for specific purposes and are intended for three specific primary audiences: prescribers, pharmacists, and patients.

From the outset, healthcare professionals such as physicians and pharmacists will be alerted to the risks of this new product, will be provided product labeling, and will be educated about the product's approved indication as well as about the definition of "opioid-tolerant" as described in the package insert. Inclusion of the risk information in the label will assure consistency of the risk warning in a variety of media including all promotional materials.

Tools directed toward prescribers will include, but are not limited to, introductory letters, visits and assessments by Cephalon field representatives, educational monographs, and targeted education and outreach programs directed to Pain Centers of Excellence and professional societies.

Tools directed toward pharmacists also will include introductory letters (PharmAlert) and visits by Cephalon field representatives. In addition, counseling messages will be distributed to pharmacies by major publishers of pharmacy counseling software. A reminder checklist is printed on the carton to prompt the pharmacist at the point of dispensing to make sure the patient is opioid tolerant before dispensing TRADE NAME and to encourage the patient to read the TRADE NAME Medication Guide.

The Medication Guide describes for the patient, in understandable non-technical language, the serious risks associated with effervescent fentanyl tablets. It provides information necessary for the patient to use the product safely and effectively. Patients will also benefit from the use of written counseling aids provided by Cephalon to physicians and pharmacists. These aids will encourage an open dialogue about TRADE NAME between the healthcare professional and the patient, thereby encouraging active participation of the patient in his/her medical care.

Table 2 summarizes the interventions that will be employed to minimize the risk of TRADE NAME being used by opioid non-tolerant individuals. It describes each of the tools and the audiences applicable to each of the interventions.

The surveillance and monitoring activities associated with the proactive interventions described above is located in section 0 and Table 5.

Table 2: Goal 1 Summary Table

Goal 1: TRADE NAME should be used only by opioid-tolerant individuals					
Goal	**Point(s) of Intervention**	**Primary Audience(s)**	**Tool Category**	**Tools**	**Description**
1	Patient Use	Patients	Targeted Education & Outreach	Blister label	Launch and Ongoing: The blister label (dome side) will contain important warning information ("Only for patients already taking opioids")
1	Dispensing Patient Use	Patients Pharmacists	Targeted Education & Outreach; Reminder system	Carton label	Launch and ongoing: The labeling of the carton contains important warning information ("Only for patients already taking opioids such as fentanyl or morphine;" and "TRADE NAME contains medicine that could be harmful or fatal to someone who has not been prescribed TRADE NAME."). A reminder checklist is printed on the carton to prompt the pharmacist to advise the patient that TRADE NAME should be used only by opioid tolerant individuals and to encourage the patient to read the Medication Guide. The carton label directs the patient and/or caregiver to read the enclosed Medication Guide for important warnings.
1	Prescribing Dispensing Patient Use	Patients Pharmacists Prescribers	Targeted Education & Outreach	Medication guide	Launch and ongoing: The TRADE NAME Medication Guide will emphasize the need for the patient to be opioid-tolerant. It will warn the patient of the potentially serious consequences, including death, of using TRADE NAME if not opioid tolerant. It will be included in the TRADE NAME packaging and will also be made available to all prescribers and TRADE NAME stocking pharmacies (via 800#, a product-specific website, and Cephalon sales representatives) for education and dissemination to patients.

(continued)

Table 2: Goal 1 Summary Table (Continued)

Goal 1: TRADE NAME should be used only by opioid-tolerant individuals					
Goal	**Point(s) of Intervention**	**Primary Audience(s)**	**Tool Category**	**Tools**	**Description**
1	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Package insert	Launch and ongoing: The package insert will contain a Boxed Warning about the life-threatening risks associated with the use of TRADE NAME in opioid non-tolerant individuals. It will define opioid tolerance.
1	Prescribing	Prescribers	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch and ongoing: Prescribers will be informed in person of the key messages and elements of the TRADE NAME RiskMAP, including the potentially life-threatening risk of use of TRADE NAME by an individual not tolerant to opioids.
1	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Educational introductory letter to healthcare professionals	Launch: Cephalon will develop and disseminate an educational TRADE NAME introductory letter which will reinforce the use of TRADE NAME only by opioid-tolerant individuals. The letter will be disseminated by direct mail to 10,000 physicians likely to prescribe TRADE NAME and 3,000 pharmacists likely to stock TRADE NAME, the top 25 Pain Centers of Excellence.
1	Prescribing	Prescribers	Targeted Education & Outreach	Educational monograph for physicians	Launch: Cephalon will develop and disseminate an TRADE NAME educational monograph which will reinforce the use of TRADE NAME only by opioid-tolerant individuals. The monograph will be disseminated by direct mail to 10,000 physicians likely to prescribe TRADE NAME and to the top 25 Pain Centers of Excellence.
1	Dispensing	Pharmacists	Targeted Education & Outreach	PharmAlert	Launch: Educational material that reinforces the use of TRADE NAME only in opioid-tolerant individuals will be distributed to 40,000 retail pharmacists.

(continued)

Table 2: Goal 1 Summary Table (Continued)

Goal 1: TRADE NAME should be used only by opioid-tolerant individuals					
Goal	**Point(s) of Intervention**	**Primary Audience(s)**	**Tool Category**	**Tools**	**Description**
1	Prescribing	Prescribers	Targeted Education & Outreach	Physician education directed to Pain Centers of Excellence	Launch: Cephalon will contact each of the identified top 25 Pain Centers of Excellence to offer further educational opportunities to learn about TRADE NAME, including the risks of use by opioid non-tolerant individuals. The educational platform for these offerings will include symposia and/or teleconferences and will incorporate the key messages of the TRADE NAME RiskMAP.
1	Dispensing Patient Use	Pharmacists Patients	Targeted Education & Outreach	Counseling messages	Launch and ongoing: Cephalon will provide risk information to First Data Bank and/or other major publishers of pharmacy counseling software to educate the majority of retail pharmacists on the risks associated with the use of TRADE NAME, including the risk of its use by opioid non-tolerant individuals.
1	Prescribing Dispensing Patient Use	Patients Pharmacists Prescribers	Targeted Education & Outreach	Counseling aids	Launch and ongoing: In addition to the Medication Guide, Cephalon will develop a counseling aid to be used by healthcare professionals when advising and educating patients about TRADE NAME. This aid will include information about the risk and potentially life-threatening consequences of use of TRADE NAME by individuals not tolerant to opioids.
1	Prescribing	Prescribers	Targeted Education & Outreach	Physician education (targeted to members of professional societies)	Launch: Professional societies will be contacted to offer educational opportunities to learn about TRADE NAME and key messages and risks described in the RiskMAP, including the risk of the use of TRADE NAME by opioid non-tolerant individuals. The educational platform for these offerings will include symposia at the professional society's meeting(s) and/or teleconferences with interested members.

(continued)

Table 2: Goal 1 Summary Table (Continued)

Goal 1: TRADE NAME should be used only by opioid-tolerant individuals					
Goal	**Point(s) of Intervention**	**Primary Audience(s)**	**Tool Category**	**Tools**	**Description**
1	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Pharmaceutical compendia	Launch and ongoing: Cephalon will provide TRADE NAME information (including risk information about its use in opioid non-tolerant individuals) to well-known drug compendia such as the Physicians' Desk Reference (PDR), American Hospital Formulary Service (AHFS), and Drug Facts and Comparisons.
1	Dispensing	Pharmacists	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch: Pharmacists likely to dispense TRADE NAME will be informed in person of the key messages and elements of the TRADE NAME RiskMAP, including the potentially life-threatening risk of use of TRADE NAME by individuals not tolerant to opioids. The pharmacists will be alerted to the utility of the Medication Guide
1	Dispensing	Pharmacists	Targeted Education & Outreach	Counseling aid	Launch and ongoing: Educational materials will be disseminated to pharmacists who attend wholesaler trade shows and pharmacy meetings. These materials will provide education that TRADE NAME should be used only by opioid-tolerant patients.
1	Prescribing	Prescribers	Targeted Education & Outreach	Speaker training	Launch and ongoing: Cephalon will formally train speakers on aspects of TRADE NAME consistent with the risk information in the package insert including the key elements and messages of the RiskMAP, specifically the risk of use in opioid non-tolerant patients will be reviewed. Cephalon will also provide speakers with information which they must present, that focus on the risks identified in the RiskMAP. Prior to speaking on behalf of Cephalon, these speakers will verify that they understand the risk associated with use of TRADE NAME in opioid non-tolerant patients. Evaluations will be provided to verify that the speakers presented the required risk information.

Table 2: Goal 1 Summary Table (continued)

Goal 1: TRADE NAME should be used only by opioid-tolerant individuals					
Goal	**Point(s) of Intervention**	**Primary Audience(s)**	**Tool Category**	**Tool**	**Description**
1	Prescribing Dispensing	Cephalon field representatives	Targeted Education & Outreach	Training for Cephalon field representatives	Launch and ongoing: Cephalon field representatives will receive product-specific training covering the approved prescribing information for TRADE NAME, including the TRADE NAME RiskMAP and the use of TRADE NAME in opioid non-tolerant patients. Upon completion of training, field representatives will be tested on the training and will be required to verify they understand the information included in the TRADE NAME RiskMAP.

Strategy and Tools Associated with Goal 2: Misuse, abuse and diversion of TRADE NAME should not occur

The risks of misuse, abuse and diversion are inherent with CII opioid drugs. To successfully address this risk in an environment where prescription drug abuse rates have been growing over the past several years requires a combination of efforts including supply chain integrity activities, educational interventions, and ongoing surveillance and monitoring activities. Law enforcement agencies also play a significant role in limiting illicit activities associated with abuse and diversion. Healthcare professionals (eg, physicians, pharmacists, nurses) who deal with Schedule II opiates should be versed in Federal, state, and local legal and regulatory requirements governing their use.

The listing of TRADE NAME under Schedule II of the Controlled Substance Act is one of the principal tools that will aid in limiting the degree to which the medication is abused and diverted. Federal and state laws and regulations govern the manufacturing, distribution, prescribing, dispensing, storage, and disposal of CII products, and there are extensive controls, record keeping requirements, and auditing functions in place to minimize the risk of abuse and diversion. For example, prescriptions for CII products must be written in ink, or typewritten and signed by the practitioner. Verbal prescriptions must be confirmed in writing within 72 hours, and may be given only in a genuine emergency. No renewals are permitted.

In evaluating the tools to reduce the risk of misuse, abuse and diversion associated with the use of TRADE NAME, Cephalon identified several points of intervention in the product's safe-product-use pathway (see Glossary). The early part of this supply chain is most directly under Cephalon's control because of the Company's internal standard operating procedures (SOPs) and auditing capabilities. Controls are applied from the time Cephalon is in receipt of fentanyl citrate throughout the manufacturing and packaging of the finished product, and through distribution to wholesalers.

To help minimize the risk of diversion of TRADE NAME, Cephalon will track every shipment of TRADE NAME from its manufacturing sites to its receipt at the wholesaler. Drug accountability will be maintained to ensure diversion has not occurred from the time the product departs from Cephalon to when it is received by the wholesaler. Wholesalers who purchase product from Cephalon will be alerted to the goals of the TRADE NAME RiskMAP, and the wholesalers will verify that they have processes and procedures in place to minimize the risk of diversion when the product is received by the pharmacies.

Given the control Cephalon has over its supply chain, opportunities for departures from the safe-use pathway are likely to increase for TRADE NAME after it leaves the Cephalon supply chain. This suggests the need for additional efforts at the following points of intervention: point of prescribing, dispensing, patient use, and disposal of the product.

At the point of prescribing, physicians should use caution when prescribing TRADE NAME to patients and should be aware of circumstances, symptoms, and signs that could contribute to an individual's risk of abuse. Persons at increased risk for opioid

abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (eg, major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed effervescent fentanyl. All patients receiving effervescent fentanyl should be routinely monitored for signs of misuse, abuse, and addiction. Physicians should also be familiar with methods used by individuals to obtain schedule II opiates illicitly (eg, doctor shopping, feigning illness or pain). For any given patient, physicians considering the use of TRADE NAME should balance the risks of product misuse, abuse, and diversion with the important medical need to adequately treat pain.

Similarly, at the point of dispensing, pharmacists should also exercise caution when dispensing TRADE NAME to patients. Pharmacists, too, should have familiarity with factors that could contribute to an individual's risk of abuse, and should be knowledgeable about methods used by individuals to obtain schedule II opiates illicitly (eg, fraudulent prescriptions, pharmacy theft).

Patients should be aware that TRADE NAME contains a schedule II opioid pain medication and that they may become addicted to this class of medications. They should be counseled that their risk for abuse and addiction may be higher if they have a history of abuse of other medications, street drugs, or alcohol, or if they have a history of mental illness. Patients should also be counseled that TRADE NAME contains a federally controlled substance and that to sell or give their medication to others is a violation of the law. Patients should also be advised that they could become targets for those who abuse prescription medications or street drugs, and that they should always store TRADE NAME in a safe place.

Tools will be employed at each of these points of intervention to minimize the risk of abuse and diversion. To inform physicians of these risks, for example, TRADE NAME monographs will be distributed and educational programs will be targeted to members of professional societies. Another example of a tool designed to aid the pharmacist as well as other healthcare professionals in this area is the use of well-known pharmaceutical compendia which will highlight the high abuse potential of TRADE NAME. The PharmAlert system will be used to target education and outreach efforts to pharmacists. The Medication Guide is an example of a tool intended for patients that conveys important information about misuse, abuse, and diversion in non-technical, scientifically accurate language.

Surveillance and monitoring activities for abuse and diversion will be discussed in section 0 and Table 5.

Table 3 provides a list of interventions, a description of each of the tools, and the audiences applicable to each of the interventions to minimize the risk of misuse, abuse, and diversion of TRADE NAME

Table 3: Goal 2 Summary Table

Goal 2: Misuse, abuse and diversion of TRADE NAME should not occur					
Goal	**Point(s) of Intervention**	**Audience**	**Tool Category**	**Tools**	**Description**
2	Dispensing Patient Use	Patients Pharmacists	Targeted Education & Outreach; Reminder system	Carton label	Launch and ongoing: The labeling of the carton contains several items of information intended to decrease misuse of the product (eg, "For Buccal Administration. Do not Swallow Tablet"). In addition the carton label advises the patient and/or caregiver to read the enclosed Medication Guide for important warnings and directions. The checklist on the carton reminds the pharmacist to counsel the patient about the use of TRADE NAME and to encourage the patient to read the TRADE NAME Medication Guide (which provides important warnings and directions). Similarly, the CII scheduling status of TRADE NAME is noted prominently on the carton to remind the pharmacist that TRADE NAME has a high potential for abuse.
2	Prescribing Dispensing Patient Use	Patients Pharmacists Prescribers	Targeted Education & Outreach	Medication guide	Launch and ongoing: The TRADE NAME Medication Guide provides information to the patient intended to minimize misuse, abuse, and diversion. It includes, for example, a section titled "How should I take "TRADE NAME." which provides instructions on proper administration of the buccal tablet. As for abuse, it warns that the patient may become physically dependent on opioids and could become addicted to TRADE NAME. For diversion, it warns patients that TRADE NAME is a federally controlled substance, that selling the medication or giving it away is against the law, and that the medication should be kept in a safe place to protect it from being stolen. The Medication Guide will be included in the TRADE NAME packaging and will also be made available to all prescribers and TRADE NAME stocking pharmacies (via 800#, a product-specific website, and Cephalon sales representatives) for education and dissemination to patients.

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Table 3: Goal 2 Summary Table (Continued)

Goal 2: Misuse, abuse and diversion of TRADE NAME should not occur					
Goal	**Point(s) of Intervention**	**Audience**	**Tool Category**	**Tools**	**Description**
2	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Package insert	Launch and ongoing. The package insert will contain information about opioid misuse, abuse, diversion, and addiction and can serve as a useful reference to healthcare professionals.
2	Prescribing	Prescribers	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch and ongoing: Prescribers will be informed in person of the key messages and elements of the TRADE NAME RiskMAP, including information on the high potential for TRADE NAME abuse as well as of its risk of misuse and diversion.
2	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Educational introductory letter to healthcare professionals	Launch: Cephalon will develop and disseminate an educational TRADE NAME introductory letter which will reinforce key messages of the RiskMAP including the risk for TRADE NAME misuse, abuse, and diversion. The letter will be disseminated by direct mail to 10,000 physicians likely to prescribe TRADE NAME, 3,000 retail pharmacists likely to stock TRADE NAME, and the top 25 Pain Centers of Excellence.
2	Prescribing	Prescribers	Targeted Education & Outreach	Educational monograph for physicians	Launch: Cephalon will develop and disseminate an TRADE NAME educational monograph which will reinforce messages about the risk of misuse, abuse, and diversion of TRADE NAME The monograph will be disseminated by direct mail to 10,000 physicians likely to prescribe TRADE NAME and to the top 25 Pain Centers of Excellence
2	Dispensing	Pharmacists	Targeted Education & Outreach	PharmAlert	Launch: Educational material that reinforces the use of TRADE NAME is associated with a risk of misuse, abuse, and diversion. This material will be distributed to 40,000 retail pharmacists.
2	Prescribing	Prescribers	Targeted Education & Outreach	Physician education directed to Pain Centers of Excellence	Launch: Cephalon will contact each of the identified top 25 Pain Centers of Excellence to offer further educational opportunities to learn about TRADE NAME, including its risks for misuse, abuse, and diversion. The educational platform for these offerings will include symposia and/or teleconferences and will incorporate the key messages of the TRADE NAME RiskMAP.

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Table 3: Goal 2 Summary Table (Continued)

Goal 2: Misuse, abuse and diversion of TRADE NAME should not occur					
Goal	**Point(s) of Intervention**	**Audience**	**Tool Category**	**Tools**	**Description**
2	Prescribing Dispensing Patient Use	Prescribers Pharmacists Patients	Targeted Education & Outreach	Counseling aid	Launch and ongoing: Cephalon will develop a counseling aid to be used by healthcare professionals when advising and educating patients about TRADE NAME. This aid will include information about the risks for misuse, abuse, and diversion.
2	Dispensing	Pharmacists	Targeted Education & Outreach	Counseling aid	Launch and ongoing: Education materials will be disseminated to pharmacists who attend wholesaler trade shows and pharmacy meetings. These materials will provide education that the use of TRADE NAME is associated with misuse, abuse and diversion.
2	Dispensing Patient Use	Pharmacists Patients	Targeted Education & Outreach	Counseling messages	Launch and ongoing: Cephalon will provide risk information to First Data Bank and/or other major publishers of pharmacy counseling software to educate the majority of retail pharmacists on the risks of misuse, abuse, and diversion associated with the use of TRADE NAME.
2	Prescribing	Prescribers	Targeted Education & Outreach	Physician education (targeted to members of professional societies)	Launch: Professional societies will be contacted to offer educational opportunities to learn about TRADE NAME and key messages and risks described in the RiskMAP, including the risk for misuse, abuse, and diversion. The educational platform for these offerings will include symposia at the professional society's meeting(s) and/or teleconferences with interested members.
2	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Pharmaceutical compendia	Launch and ongoing: Cephalon will provide TRADE NAME information (including risk information about its misuse, abuse and diversion) to well-known drug compendia such as the Physicians' Desk Reference (PDR), American Hospital Formulary Service (AHFS), and Drug Facts and Comparisons.

(continued)

Table 3: Goal 2 Summary Table (Continued)

Goal 2: Misuse, abuse and diversion of TRADE NAME should not occur					
Goal	**Point(s) of Intervention**	**Audience**	**Tool Category**	**Tools**	**Description**
2	Prescribing	Prescribers	Targeted Education & Outreach	Speaker training	Launch and ongoing: Cephalon will formally train speakers on aspects of TRADE NAME consistent with the risk information in the package insert including the key elements and messages of the RiskMAP, specifically the risk of misuse, abuse and diversion associated with use of TRADE NAME. Cephalon will also provide speakers with information, which they must present, that focus on the risks identified in the RiskMAP. Prior to speaking on behalf of Cephalon, these speakers will verify they understand the risk of misuse, abuse and divserion associated with use of TRADE NAME. Evaluations will be provided to verify that the speakers presented the required risk information.
2	Prescribing	Prescribers and Pharmacists	Targeted Education & Outreach	Physician and Pharmacist education	Ongoing (response to surveillance): Cephalon will implement medical education directed to 'geographic hot spots' that focus on preventing and/or minimizing misuse, abuse, and diversion of prescription drugs. The format of these programs will be tailored to the specific need (eg, symposium, teleconferences, print materials, etc.)
2	Prescribing Dispensing	Cephalon field representatives	Targeted Education & Outreach	Training for Cephalon field representatives	Launch and ongoing: Cephalon field representatives will receive product-specific training covering the approved prescribing information for TRADE NAME, including the TRADE NAME RiskMAP and the risk for misuse, abuse and diversion associated with use of TRADE NAME. Upon completion of training, field representatives will be tested on the training and will be required to verify they understand the information included in the RiskMAP.
2	Prescribing Dispensing	Prescriber Pharmacists	Targeted Education & Outreach	Independent continuing medical education (CME)	Launch: Cephalon will support independent education on prescription drug misuse, abuse, and diversion targeted to physicians likely to prescribe TRADE NAME.

Table 3: Goal 2 Summary Table (Continued)

Goal 2: Misuse, abuse and diversion of TRADE NAME should not occur					
Goal	**Point(s) of Intervention**	**Audience**	**Tool Category**	**Tools**	**Description**
2	Prescribing Dispensing Patient Use	Drug Diversion Professionals	Targeted Education & Outreach	Introductory Letter to Drug Diversion Authorities	Launch: Proactive communications to drug diversion control authorities to educate interested parties and alert them to safeguard against the potential diversion of TRADE NAME.
2	Dispensing	Pharmacists	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch: Pharmacists likely to dispense TRADE NAME will be informed in person of the key messages and elements of the TRADE NAME RiskMAP, including the risks for misuse, abuse, and diversion for TRADE NAME. The pharmacists well be alerted to the utility of the Medication Guide.
2	Patient Use	Patients	Targeted Education & Outreach	Product returns and Disposal	Launch and ongoing: Cephalon will accept returns for disposal of unwanted TRADE NAME. This will be a tool to minimize the amount of excess product available.
2	Prescribing Dispensing Patient Use	Drug Diversion Professionals	Active Monitoring	Reports of Diversion and Abuse	Launch and ongoing: Cephalon will attempt to implement an active monitoring system (eg, RADARS) at the time of the launch of TRADE NAME. Reports form the National Association of Drug Diversion Investigators (NADDI) will be actively monitored and screened for information on TRADE NAME.

Strategy and Tools Associated with Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur

In contrast to ACTIQ, a transmucosal fentanyl lozenge on a handle, the tablet formulation and packaging of TRADE NAME is not expected to be intrinsically more interesting or appealing to children than tablet formulations in blister packaging of other drugs. Nonetheless, there is a risk of serious harm should a child (or cognitively impaired adult) be accidentally exposed to TRADE NAME. Consequently, Cephalon has defined a safe product use pathway that seeks to minimize the occurrence of unintended or accidental exposure to TRADE NAME in adults or children. It consists of explicit instructions and control measures that describe the safe use of the product at appropriate intervention points including during transit in the supply chain, at the point of prescribing, at the point of dispensing, during consumer storage and at the point of disposal of product. These instructions will be incorporated into product labeling and will be the first line of defense in the prevention of unintended TRADE NAME ingestions. Interventions will be introduced at the time of commercialization, and will be considered again once data have been accumulated to evaluate the extent of risk. Modifications to the tools employed in the RiskMAP may be made as appropriate.

Note that at the point of home storage, the TRADE NAME child-resistant packaging provides protection from departures from the safe product use pathway. Specifically, the TRADE NAME blister packaging has met the effectiveness specifications using the Child Test procedure for special packaging (16 CFR 1700.20(a)(2)) and has met performance specifications for an “F1” classification (see Glossary) (see Appendix B).

Table 3 provides a list of interventions, a description of each of the tools, and the audiences applicable to each of the interventions to minimize the risk of accidental exposure to TRADE NAME.

Surveillance and monitoring activities for unintended exposure will be discussed in section 0 and Table 5.

Table 4: Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur

Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Patient use	Patients	Package integrity	Blister	Launch and ongoing: Tablets will be supplied in double foil blister which meet F1 requirements and which have passed tests for child resistance and senior friendliness. This tool is designed to minimize the risk of accidental exposure to TRADE NAME.
3	Patient use	Patients	Targeted Education & Outreach	Blister label	Launch and ongoing: The blister label warns that TRADE NAME is to be kept out of the reach of children. It instructs that TRADE NAME should be used immediately upon opening. These tools are designed to minimize the risk of accidental exposure to TRADE NAME.
3	Dispensing Patient use	Pharmacists Patients	Targeted Education & Outreach Reminder System	Carton label	Launch and ongoing: The carton labeling contains several items of information intended to decrease the risk of accidental exposure to TRADE NAME. It warns that TRADE NAME is to be kept out of the reach of children and that TRADE NAME contains medicine that could be harmful or fatal to someone who has not been prescribed the medicine. In addition, the carton label advises the patient and/or caregiver to read the enclosed Medication Guide for important warnings and directions. The checklist on the carton reminds the pharmacist to encourage the patient to read the TRADE NAME Medication Guide (which provides important warnings and directions about accidental exposure)

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Table 4: Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur (Continued)

Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Prescribing Dispensing Patient use	Prescribers Pharmacists Patients	Targeted Education & Outreach	Medication Guide	Launch and ongoing: The TRADE NAME Medication Guide provides information to the patient intended to decrease the risk of accidental exposure to TRADE NAME. It warns that TRADE NAME is to be kept in a safe place away from children, and that accidental use by a child is a medical emergency that can result in death. In the event of accidental use by a child, the Medication Guide provides instructions for contacting a Poison Control Center or the nearest emergency room right away. The Medication Guide will be included in the TRADE NAME packaging and will also be made available to all prescribers and TRADE NAME stocking pharmacies (via 800#, a product-specific website, and Cephalon sales representatives) for education and dissemination to patients.
3	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Package insert	Launch and ongoing: The package insert contains a Boxed Warning for healthcare professionals about the risks associated with the accidental exposure to TRADE NAME.
3	Prescribing	Prescribers	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch and ongoing: Prescribers will be informed in person of the key messages and elements of the TRADE NAME RiskMAP, including the potentially life-threatening risk of accidental use of TRADE NAME in children or adults.

(continued)

Table 4: Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur (Continued)

Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Dispensing	Pharmacists	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch: Pharmacists likely to dispense TRADE NAME will be informed in person of the key messages and elements of the TRADE NAME RiskMAP, including the potentially life-threatening risk of accidental use of TRADE NAME in children or adults. The pharmacists will be alerted to the utility of the Medication Guide
3	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Educational introductory letter to healthcare professionals	Launch: Cephalon will develop and disseminate an educational TRADE NAME introductory letter which will reinforce key messages of the RiskMAP including the risk of accidental exposure to TRADE NAME. The letter will be disseminated by direct mail to 10,000 physicians likely to prescribe TRADE NAME, 3,000 retail pharmacists likely to prescribe TRADE NAME, and the top 25 Pain Centers of Excellence.
3	Prescribing	Prescribers	Targeted Education & Outreach	Educational monograph for physicians	Launch: Cephalon will develop and disseminate an TRADE NAME educational monograph which will reinforce messages about the risk of accidental exposure to TRADE NAME The monograph will be disseminated by direct mail to 10,000 physicians likely to prescribe TRADE NAME and to the top 25 Pain Centers of Excellence.

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Table 4: Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur (Continued)

Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Dispensing	Pharmacists	Targeted Education & Outreach	PharmAlert	Launch: Educational material that explains the risk of accidental exposure associated with the use of TRADE NAME.
3	Prescribing	Prescribers	Targeted Education & Outreach	Physician education directed to Pain Centers of Excellence	Launch: Cephalon will contact each of the identified top 25 Pain Centers of Excellence to offer further educational opportunities to learn about TRADE NAME, including the risks of accidental exposure associated with the use of TRADE NAME. The educational platform for these offerings will include symposia and/or teleconferences and will incorporate the key messages of the RiskMAP.
3	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Pharmaceutical compendia	Launch and ongoing: Cephalon will provide TRADE NAME information (including risk information about the risk of accidental exposure to TRADE NAME) to well-known drug compendia such as the Physicians' Desk Reference (PDR), American Hospital Formulary Service (AHFS), and Drug Facts and Comparisons
3	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Counseling messages	Launch and ongoing: Cephalon will provide risk information to First Data Bank and/or other major publishers of pharmacy counseling software to educate the majority of retail pharmacists in the risks associated with the use of TRADE NAME, including the risk of accidental exposure associated with its use.

(continued)

Table 4: Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur (Continued)

Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Prescribing Dispensing Patient Use	Prescribers Pharmacists Patients	Targeted Education & Outreach	Counseling aid	Launch and ongoing: In addition to the Medication Guide, Cephalon will develop a counseling aid to be used by healthcare professionals when advising and education patients about TRADE NAME. This aid will include information about the risk and potentially life-threatening consequences associated with the accidental use of TRADE NAME.
3	Dispensing	Pharmacists	Targeted Education & Outreach	Counseling aid	Launch and ongoing: Educational materials will be disseminated to pharmacists who attend wholesaler trade shows and pharmacy meetings. These materials will provide education that accidental exposure is associated with the use of TRADE NAME.
3	Prescribing	Prescribers	Targeted Education & Outreach	Speaker training	Launch and ongoing: Cephalon will formally train speakers on aspects of TRADE NAME consistent with the risk information in the package insert including the key elements and messages of the RiskMAP, specifically the risk of accidental exposure to TRADE NAME. Cephalon will also provide speakers with information, which they must present, that focus on the risks identified in the RiskMAP. Prior to speaking on behalf of Cephalon, these speakers will verify they understand the risk of accidental exposure associated with the use of TRADE NAME. Evaluations will be provided to verify that the speakers presented the required risk information.

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Table 4: Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur (Continued)

Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Prescribing Dispensing	Cephalon field representatives	Targeted Education & Outreach	Training for Cephalon field representatives training	Launch and ongoing: Cephalon field representatives will receive product-specific training covering the approved prescribing information for TRADE NAME, including the TRADE NAME RiskMAP. Upon completion of training, field representatives will be tested on the training and will be required to verify they understand the information included in the TRADE NAME RiskMAP.
3	Patient Use	Patients	Targeted Education & Outreach	Product returns and Disposal	Launch and ongoing: Cephalon will accept returns for disposal of unwanted TRADE NAME. This will be a tool to minimize the amount of excess product available.
3	Patient Use	Patients	Targeted Education & Outreach	Toll-free number	Launch and ongoing: Poison control number for accidental ingestion.

Measuring Effectiveness of The RiskMAP

The RiskMAP is designed to address three principal risks associated with TRADE NAME: 1) its use by opioid non-tolerant individuals, (2) the risk of misuse, abuse, and diversion, and 3) unintended (accidental) exposure to the product. The effectiveness of the tools identified in this RiskMAP will be evaluated on an ongoing basis.

A principal goal of the RiskMAP is to ensure that physicians, pharmacists, and patients are aware and knowledgeable of these risks and are aware of steps they can take to minimize them. Cephalon will employ a series of independent and unique surveillance and monitoring techniques targeted at prescribers, pharmacists, and patients, respectively, to assess the effectiveness of the targeted education and reminder systems at the points of intervention. The surveillance and monitoring activities associated with the TRADE NAME RiskMAP may be found in Table 5.

Active and Passive Surveillance Systems

Reports of spontaneous adverse events are valuable since they provide an understanding of behaviors associated with the use of a product in actual use. Databases such as TESS and DAWN and monitoring of publications will be utilized to augment Cephalon's pharmacovigilance system. Data obtained from passive reporting systems, however, may be biased toward capturing certain outcomes or can result in delays in signal detection. True rates cannot be accurately ascertained from such systems. However, Cephalon is considering employing an active surveillance system (similar or the same as RADARS) to identify the use patterns of the product to compensate for the limitations of spontaneous adverse event reporting (see section 0 and Table 2).

Surveys

Another surveillance tool utilized in the TRADE NAME RiskMAP will be the use of three separate survey systems targeted at the three principal intended audiences: prescribers, pharmacists and patients. As with any methodology, there are a number of potential limitations to use of surveys. However, a well-designed survey using appropriate controls to minimize bias could help compensate for the limitations associated with this methodology, enabling one to capture valuable measurements for assessment.

Physician Surveys

Surveys of physicians will be employed to evaluate prescribing patterns. Whereas several databases provide broad descriptive data, databases such as the NCI and IMS databases have inherent limitations in being able to evaluate physician prescribing patterns. For instance, the data are limited in that one cannot obtain the reason why a drug has been prescribed. For example, this could limit the ability to evaluate whether the practitioner is prescribing TRADE NAME to opioid tolerant patients. Surveys provide detailed information providing insight into data captured by such databases.

To provide more specific evaluative information, a sample of physicians will be selected for surveying: This survey(s) will include assessments in the following areas:

- their knowledge of the key risks associated with the use of TRADE NAME,

- their knowledge of the indication for TRADE NAME,
- their patterns of TRADE NAME prescribing (eg, opioid tolerant vs. opioid non-tolerant),
- their assessment of the risk minimization tools (eg, use of, and reaction to, various Cephalon communications),

The physician survey(s) will serve to monitor physicians' knowledge of and use of TRADE NAME. It will also monitor the awareness of prescribers to the risks associated with the use of the product in patients not-tolerant to opioids. Responses to these questions and others will be important to help understand whether adjustments in interventions or key messages will be needed to improve the RiskMAP over time.

The physician survey(s) will be repeated every six months for the first two years of the program, at which time internal and external experts associated with Cephalon will evaluate the results. Following review of the survey(s), questions and time frames may be modified.

Pharmacy Surveys

A survey targeting the dispensing pharmacists will also be employed. This survey will include assessments in the following areas:

- their knowledge of the key risks associated with the use TRADE NAME,
- their knowledge of the indication for TRADE NAME,
- their awareness and use of the carton checklist, Medication Guide, and other information about the product made available by Cephalon field representatives, and
- their assessment of the value of counseling messages provided by major publishers of pharmacy counseling software.

Patient Surveys

Finally, a patient survey will be employed to evaluate the RiskMAP tools. This survey will include assessments in the following areas:

- their knowledge of the key risks associated with the use TRADE NAME,
- their knowledge of the indication for TRADE NAME,
- their knowledge about the directions for use of TRADE NAME, and
- their receipt of, and perceived utility of, the Medication Guide and other counseling tools for TRADE NAME.

The pharmacist and patient surveys will be repeated every six months for the first two years of the program and trends will be analyzed. Modifications to the RiskMAP will be made as needed.

Claims Data

Cephalon will also purchase claims data as a surveillance tool to monitor prescribing patterns and, if possible, to assess the degree to which TRADE NAME is prescribed only to opioid-tolerant patients. The feasibility of using claims data further to provide meaningful information on clinical outcomes associated with the use of TRADE NAME

will be assessed before the database is utilized for such purposes. Whereas valuable insights into the RiskMAP and clinical outcomes might be obtained with a suitable database (eg, emergency room visits due to respiratory depression, emergency room visits because of accidental pediatric exposure; hospitalizations for opioid abuse; deaths associated with use of the medication, etc.), limitations of claims databases may not allow valid or reliable assessments to be made. For example, claims databases may be too limited in size to assess uncommon or rare adverse events, particularly if TRADE NAME use is not common, if patient turnover with the database is high, if events are not accurately coded, etc. However, should feasibility studies indicate that further evaluation of claims databases would be useful, then use of the claims data for these purposes will be pursued with an objective of gaining additional insights into the performance of the RiskMAP.

Other Surveillance Activities

As a follow-up to surveillance and monitoring activities, interventions may be warranted for any one or a combination of the risks described throughout this risk management plan. For example, if significant abuse or diversion is identified as occurring in a geographic area, Cephalon may employ education initiatives, as well as the use of local media and other communication vehicles, such as community outreach programs, to inform the community about the dangers and laws surrounding prescription opioid abuse.

Healthcare practitioners will be educated proactively and reactively on identifying patients who may be “doctor shopping” and/or have the potential for misuse and abuse of TRADE NAME. For example, a response after identification of a ‘geographic hot spot’ may be to follow-up with the prescriber(s) within that vicinity with a letter reminding them of TRADE NAME’s CII scheduling status, risks associated with the drug, and the implications associated with its diversion. Other interventions may include community outreach as a technique to help educate a community that may be at particular risk. Cephalon will cooperate with and assist law enforcement agencies at a federal, state, and local level in cases of abuse or diversion of TRADE NAME.

Target Values

It is not possible to determine with any degree of confidence an acceptable level of noncompliance for these goals. Rather than set an ‘a priori’ standard for acceptable compliance, Cephalon proposes to establish a quality assurance procedure.

After reviewing the data obtained from spontaneous adverse event reports, surveys, and claims-based systems, an evaluation of performance will be made. Upon analysis of each departure from the RiskMAP, the potential causes of such departures will be assessed, and, if needed, changes to the RiskMAP will be made to improve performance. Analytical tools will be used, as feasible, to facilitate the process, (eg, decision trees, criticality indices). The intent of the assessment is to identify which tools have been most effective and which ones warrant modification to increase success in achieving the objectives of the RiskMAP.

Periodic evaluations will occur to monitor progress of the RiskMAP at meeting its objectives. Areas for improvement will be identified and the RiskMAP may be modified

based on these evaluations. Specific measures (included in the evaluations) will be monitored for progress against measured performance. If sufficient progress is not made, RiskMAP modifications will be made.

Time Frames and Progress Report Submission

RiskMAP evaluations will be conducted quarterly for the first two years of marketing, with a report of the evaluations submitted to the FDA. Subsequent to this time period, assessments of the RiskMAP will be made on an annual basis and Cephalon will provide the FDA with a report of its progress and any changes they have made to the program.

Table 5: Surveillance and Monitoring Activities

Goal	Purpose	Primary Audience(s)	Tool Category	Tool	Description
1,2,3	Refine understanding of key points of intervention in FMEA analyses	FDA Cephalon	Pharmacovigilance	Spontaneous Adverse Event Reporting System	Expedited reporting of serious adverse events (SAEs) associated with abuse, misuse, or diversion.of TRADE NAME as well as SAEs associated with accidental exposure to TRADE NAME (including TESS data) or use by opioid non-tolerant individuals. Conduct periodic reviews of reports to discern any pattern(s) in departures from safe-product-use pathways of TRADE NAME.
1,2,3	Refine understanding of key points of intervention in FMEA analyses	FDA Cephalon	Pharmacovigilance	Literature Review	Regular structured review of scientific literature on (1) misuse, abuse, and diversion of TRADE NAME, (2) accidental exposures to TRADE NAME, and (3) SAEs associated with use of TRADE NAME by opioid non-tolerant individuals to discern any pattern(s) in departures from safe-product-use pathways of TRADE NAME.
2	Refine understanding of patterns of abuse or diversion of TRADE NAME	FDA Cephalon	Pharmacovigilance	Review National Surveys	National surveys on abuse and diversion, such as Drug Abuse Warning Network (DAWN), Monitoring the Future (MTF), National Survey on Drug Use and Health (NSDUH, formerly called NHDSA), will be reviewed to look for any signal or patterns of abuse or diversion associated with TRADE NAME.

(continued)

Table 5: Surveillance and Monitoring Activities (Continued)

Goal	Purpose	Primary Audience(s)	Tool Category	Tool	Description
1,2,3	RiskMAP Evaluation	FDA Cephalon	Assessment of comprehension, knowledge, attitudes, and/or desired safety behaviors about drug safety risks	Prescriber surveys	Prescribers will be surveyed to assess (1) their knowledge of the key risks associated with the use of TRADE NAME, (2) their knowledge of the indication for TRADE NAME, (3) their patterns of TRADE NAME prescribing (eg, opioid vs. non-opioid tolerant), and (4) their assessment of the risk minimization tools (eg, use of, and reaction to, various Cephalon communications).
1,2,3	RiskMAP Evaluation	FDA Cephalon	Assessment of comprehension, knowledge, attitudes, and/or desired safety behaviors about drug safety risks	Pharmacist surveys	Pharmacists will be surveyed to assess (1) their knowledge of the key risks associated with the use of TRADE NAME, (2) their knowledge of the indication for TRADE NAME, (3) their awareness and use of the carton checklist, Medication Guide, and other information about the product made available by Cephalon field representatives, and (4) their assessment of the value of counseling messages provided by major publishers of pharmacy counseling software.
1,2,3	RiskMAP Evaluation	FDA Cephalon	Assessment of comprehension, knowledge, attitudes, and/or desired safety behaviors about drug safety risks	Patient surveys	Patients will be surveyed to assess (1) their knowledge of the key risks associated with the use of TRADE NAME, (2) their knowledge of the indication for TRADE NAME, (3) their knowledge about the directions for use of TRADE NAME, and (4) their receipt of, and perceived utility of, the Medication Guide and other counseling tools for TRADE NAME.
1,2,3	RiskMAP Evaluation	FDA Cephalon	Process measures that reflect desirable safety behavior & Outcome measures	Claims data	Cephalon will evaluate, via feasibility studies, whether the purchase of claims data as a surveillance tool will provide meaningful information on clinical outcomes associated with the use of ACCLEANYL.
1,2,3	Internal Auditing	Cephalon	Validation of internal process	TRADE NAME speaker bureau training	TRADE NAME speakers will verify that they have been trained on and understand the 3 principal risks identified in the RiskMAP.
1,2,3	External Auditing	Cephalon	Validation of external process	Validation of speaker bureau communication of risks	Cephalon field personnel will verify that TRADE NAME speakers present the information that focuses on the risks identified in the RiskMAP at each TRADE NAME promotional education program.

GLOSSARY OF TERMS

Abuse: Drug abuse (limited to medicinal products only) is defined as "a persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects (Volume IX of Pharmacovigilance; The Rules of Governing Medicinal Products in the EU).

Accidental Pediatric Exposure: All accidental pediatric (children <17 years of age) exposures including misguided uses or use facilitated by a non-healthcare professional, excluding intentional recreational use by an adolescent.

Diversion: The willful transfer of a drug from legitimate supply (manufacture, distribution, or storage in hospitals, pharmacies, physicians' offices) and/or patients for whom the drug has been prescribed to unauthorized users and/or for illegal sale.

F1 packaging: Packaging that meets the effectiveness specifications using the Child Test procedure for special packaging (16 CFR 1700.20(a)(2)). The "F value" is the number of individual units (eg, tablets) to which access is obtained by a child under these testing conditions. For effervescent fentanyl tablets, access to a single 100 mcg tablet by a child could produce serious personal injury or serious illness. Under these conditions, F1 means that during such testing should a child be able to enter the package and gain access to one or more placebo test tablets, the package will fail for that particular child.

Failure Mode Effects Analysis (FMEA): A prospective procedure in which each potential failure mode in every subitem of an item is analyzed to determine its effect on other subitems and on the required function of the item.

Launch: The 6-month time period immediately following commercialization of a product, where commercialization means shipping a product to a wholesaler for subsequent distribution and sale.

Misuse: Use of a medication, prescribed by a physician, in a manner which is not prescribed.

Root-Cause Analysis: A process for identifying the basic or causal factor(s) that underlie variation in performance, including the occurrence or possible occurrence of a sentinel event.

Safe product use pathway: A set of explicit instructions and control measures that describe the safe use of the product at appropriate intervention points including at the supply chain, at the point of prescribing, at the point of dispensing, during consumer storage and at the disposal of product.

Supply chain: Begins with Cephalon's receipt of fentanyl citrate through the manufacturing and packaging of TRADE NAME.

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APPENDIX A TOOLS EMPLOYED IN THE TRADE NAME RISKMAP

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
1	Blister	Launch and ongoing: Tablets will be supplied in double-foil blister which meet F1 requirements and which have passed tests for child resistance and senior friendliness. This tool is designed to minimize the risk of accidental exposure to TRADE NAME.	Patients	3	L,O	√
2	Blister label	Launch and ongoing: The blister label contains warning information that TRADE NAME should be kept of the reach of children and that is only for patients already taking opioids; it also contains instructions for use.	Patients	1,3	L,O	√
3	Carton label	Launch and ongoing: The labeling of the carton will contain warning information, be color coded by strength, and will contain a reminder checklist to prompt the pharmacist to counsel the patient about the 3 principal risks associated with use of TRADE NAME. The carton label also directs the patient and/or caregiver to read the Medication Guide for important warnings.	Patients Pharmacists	1,2,3	L,O	√

(continued)

APPENDIX A TOOLS EMPLOYED IN THE TRADE NAME RISKMAP (CONTINUED)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
4	Medication guide	Launch and ongoing: The TRADE NAME Medication Guide will emphasize the 3 principal risks associated with the use of TRADE NAME. Specifically it warns the patient of the potentially serious consequences, including death, that may occur when using TRADE NAME in opioid non-tolerant patients; it warns that the patient may become physically dependent on opioids and could become addicted to TRADE NAME; and lastly it warns that TRADE NAME is to be kept out of the reach of children and that TRADE NAME contains medicine that could be harmful or fatal to someone who has not been prescribed the medicine. It will go directly to patients via packaging the carton and will be made available to all prescribers and TRADE NAME-stocking pharmacies (via 800#, product-specific website and Cephalon sales representatives) for education and dissemination to patients.	Patients Pharmacists Prescribers	1,2,3	L,O	√
5	Package insert	Launch and ongoing: The package insert will contain a Boxed Warning about the life-threatening risks associated with the use of TRADE NAME in opioid non-tolerant patients; misuse, abuse and diversion; and accidental exposure to the medication.	Pharmacists Prescribers	1,2,3	L,O	√
6	Direct Risk communication by Cephalon field representatives	Launch and ongoing: Prescribers will be informed in person of the key messages and elements of the TRADE NAME RiskMAP, including the potentially life-threatening risk of use by an opioid non-tolerant individual, the high potential for TRADE NAME abuse as well as the risk of misuse and diversion, and the potentially life-threatening risk of accidental use of TRADE NAME in children or adults.	Prescribers	1,2,3	L,O	√

(continued)

APPENDIX A TOOLS EMPLOYED IN THE TRADE NAME RISKMAP (CONTINUED)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
7	Direct Risk communication by Cephalon field representatives	Launch: Pharmacists likely to dispense TRADE NAME will be informed in person of the key messages and elements of the TRADE NAME Risk MAP, including the potentially life-threatening risk of use by an opioid non-tolerant individual, the high potential for TRADE NAME abuse as well as the risk of misuse and diversion, and the potentially life-threatening risk of accidental use of TRADE NAME in children or adults.	Pharmacists	1,2,3	L	√
8	Educational Introductory Letter to Healthcare Professionals	Launch: Cephalon will develop and disseminate an educational TRADE NAME introductory letter reinforcing the 3 principal messages of the RiskMAP. Specifically these messages will address that TRADE NAME is to be used only by opioid-tolerant individuals; a risk of misuse, abuse and diversion is associated with TRADE NAME; and there is a risk of accidental exposure associated with the use of TRADE NAME. At the time of launch, the letter will be disseminated via direct mail to 10,000 identified healthcare practitioner targets, 3,000 retail pharmacists likely to stock TRADE NAME, and the top 25 Pain Centers of Excellence.	Prescribers Pharmacists	1,2,3	L	√
9	Educational monograph for physicians	Launch: Cephalon will develop and disseminate a TRADE NAME educational monograph which will reinforce the 3 principal messages of the RiskMAP. Specifically these messages will address that TRADE NAME is to be used only by opioid-tolerant individuals; a risk of misuse, abuse and diversion is associated with TRADE NAME; and there is a risk of accidental exposure associated with the use of TRADE NAME. The monograph will be disseminated at launch via direct mail to 10,000 identified healthcare practitioners and the top 25 Pain Centers of Excellence.	Prescribers	1,2,3	L	√

(continued)

APPENDIX A TOOLS EMPLOYED IN THE TRADE NAME RISKMAP (CONTINUED)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
10	PharmAlert	Launch: Educational material that reinforces the 3 principal messages of the RiskMAP. Specifically these messages will address that TRADE NAME is to be used only by opioid-tolerant individuals; a risk of misuse, abuse and diversion is associated with TRADE NAME; and there is a risk of accidental exposure associated with the use of TRADE NAME. These will be distributed to 40,000 retail pharmacists.	Pharmacists	1,2,3	L	√
11	Physician education directed to Pain Centers of Excellence	Launch: Cephalon will contact each of the identified top 25 Pain Centers of Excellence to offer further educational opportunities to learn about TRADE NAME, including the 3 principal risks identified in the RiskMAP. Specifically risk of use by opioid non-tolerant individuals, the risks for misuse, abuse and diversion, and the risk of accidental exposure to TRADE NAME will be addressed. The educational platform for these offerings will include symposia and/or teleconferences.	Prescribers	1,2,3	L	√
12	Pharmaceutical compendia	Launch and ongoing: Cephalon will provide TRADE NAME information, including the 3 principal risks identified in the RiskMAP, to several well-known compendia such as Physicians' Desk Reference (PDR), American Hospital Formulary Service (AHFS), and Drug Facts and Comparisons.	Prescribers Pharmacists	1,2,3	L,O	

(continued)

APPENDIX A TOOLS EMPLOYED IN THE TRADE NAME RISKMAP (CONTINUED)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
13	Counseling messages	Launch and ongoing: Cephalon will provide risk information to First Data Bank and/or other major publishers of pharmacy counseling software to educate the majority of retail pharmacists on the 3 principal risks associated with use of TRADE NAME. Specifically these messages will address that TRADE NAME is to be used only by opioid-tolerant individuals; a risk of misuse, abuse and diversion is associated with TRADE NAME; and there is a risk of accidental exposure associated with the use of TRADE NAME.	Prescribers Pharmacists	1,2,3	L,O	√
14	Counseling aid	Launch and ongoing: In addition to the Medication Guide, Cephalon will develop a counseling aid to be used by healthcare professionals when advising and educating patients about TRADE NAME. This aid will include information about the 3 principal risks associated with use of TRADE NAME. Specifically the aid will include information addressing that TRADE NAME is to be used only by opioid-tolerant individuals; a risk of misuse, abuse and diversion is associated with TRADE NAME; and there is a risk of accidental exposure associated with the use of TRADE NAME.	Patients Pharmacists Prescribers	1,2,3	L,O	√
15	Counseling aid	Launch and ongoing: Educational materials will be disseminated to pharmacists who attend wholesaler trade shows and pharmacy meetings. These materials will provide education on the 3 principal risks identified in the RiskMAP. Specifically these materials will include information addressing that TRADE NAME is to be used only by opioid-tolerant individuals; a risk of misuse, abuse and diversion is associated with TRADE NAME; and there is a risk of accidental exposure associated with the use of TRADE NAME.	Pharmacists	1,2,3	L,O	√

(continued)APPENDIX A TOOLS EMPLOYED IN THE TRADE NAME RISKMAP (CONTINUED)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
16	Speaker training	Launch and ongoing: Cephalon will formally train speakers on aspects of TRADE NAME consistent with the risk information in the package insert, including the key elements and messages of the RiskMAP. Cephalon will also provide speakers with information which they must present, that focus on the risks identified in the RiskMAP. Prior to speaking on behalf of Cephalon, these speakers will verify that they understand the 3 principal risks associated with the use of TRADE NAME. Evaluations provided will monitor whether speakers presented the required risk information.	Prescribers	1,2,3	L,O	√
17	Training for Cephalon field representatives	Launch and ongoing: Cephalon field representatives will receive product-specific training covering the approved prescribing information for TRADE NAME, including the TRADE NAME RiskMAP. Upon completion of the training, field representatives will be tested on the training and will be required to verify their understanding of the information, including the information on the 3 principal risks identified in the RiskMAP.	Cephalon field representatives	1,2,3	L,O	√
18	Independent continuing medical education (CME)	Launch: Cephalon will support independent education on prescription drug misuse, abuse, and diversion targeted to physicians likely to prescribe TRADE NAME.	Prescribers Pharmacists	2	L	
19	Introductory Letter to Drug Diversion Authorities	Launch: Proactive communications to drug diversion control authorities to educate interested parties and alter them to safeguard against the potential diversion of TRADE NAME.	Drug diversion professionals	2	L	
20	Product returns and disposal	Launch and ongoing: Cephalon will accept returns for disposal of unwanted TRADE NAME. This will be a tool to minimize the amount of excess product available.	Patients	2,3	L,O	√

(continued)

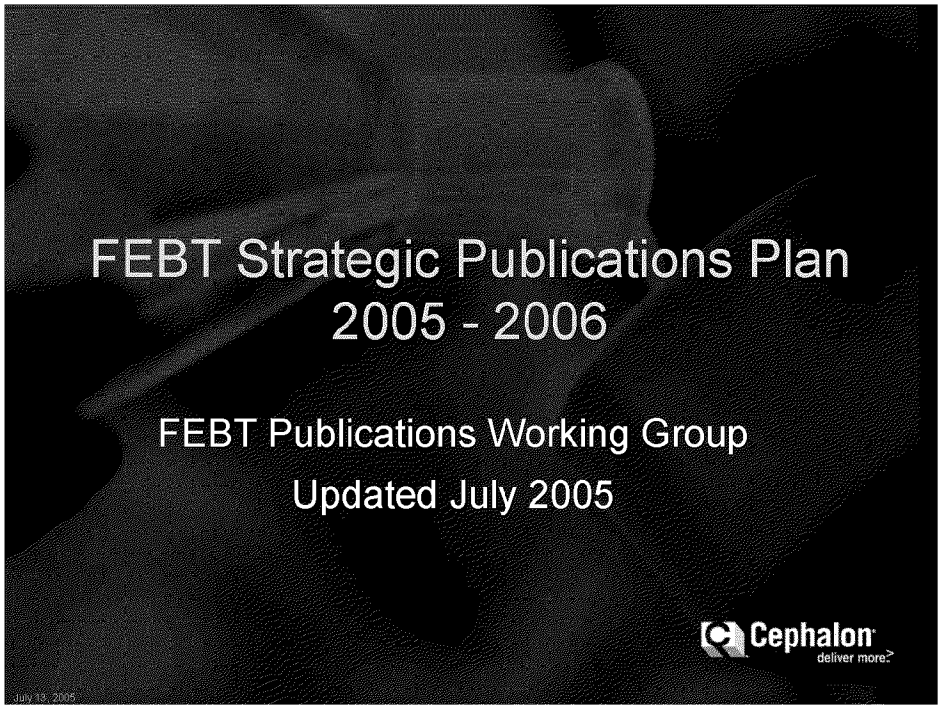
APPENDIX A TOOLS EMPLOYED IN THE TRADE NAME RISKMAP (CONTINUED)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
21	Physician and Pharmacist education	Ongoing (response to surveillance): Cephalon will implement medical education directed to 'geographic hot spots' that focus on preventing and/or minimizing misuse, abuse, and diversion of prescription drugs. The format of these programs will be tailored to the specific need (eg, symposium, teleconferences, print materials, etc.)	Prescribers Pharmacists	2	O	√
22	Toll-free number	Launch and ongoing: Poison control number for accidental ingestions.	Patients	3	L,O	
23	Reports of diversion and abuse	Launch and ongoing: Cephalon will attempt to implement an active monitoring system (eg, RADARS) at the time of the launch of TRADE NAME. Reports from the National Association of Drug Diversion Investigators (NADDI) will be actively monitored and screened for information on TRADE NAME.	Drug Diversion Professionals	2	L,O	
24	Physician education (targeted to members of professional societies)	Launch: Professional societies will be contacted to offer educational opportunities to learn about TRADE NAME and key messages and risks described in the RiskMAP, including the risk for misuse, abuse, and diversion. The educational platform for these offerings will include symposia at the professional society's meeting(s) and/or teleconferences with interested members.	Prescribers	2	L	√

APPENDIX B
CHILD RESISTANT PACKAGING PROTOCOL REPORT

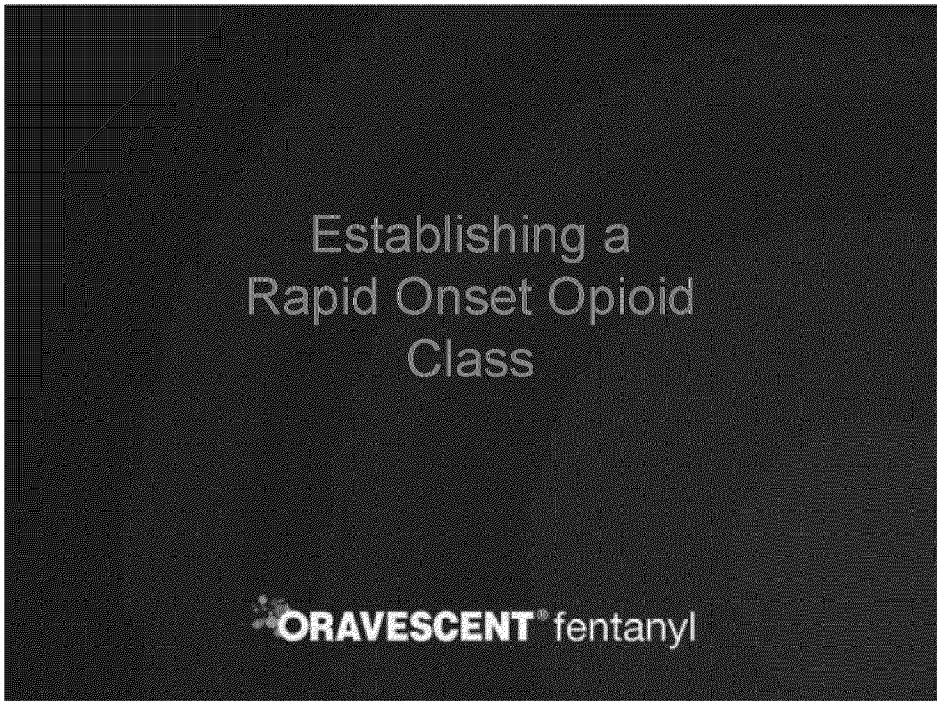
Appendix 5 – FEBT Publication/Communication Plan

NOTE: Please refer to ISCP Web site for full presentation.



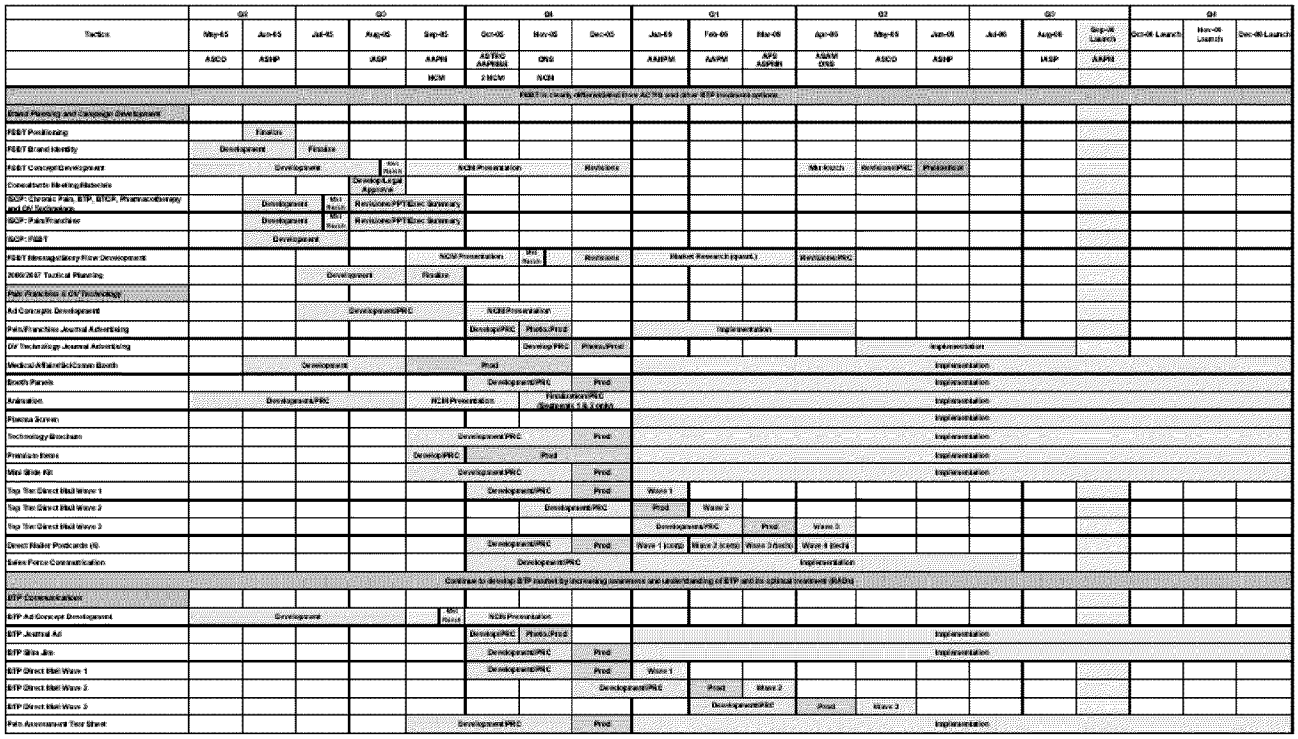
Appendix 6 – Rapid-Onset Opioid Situation

NOTE: Please refer to ISCP Web site for full presentation.



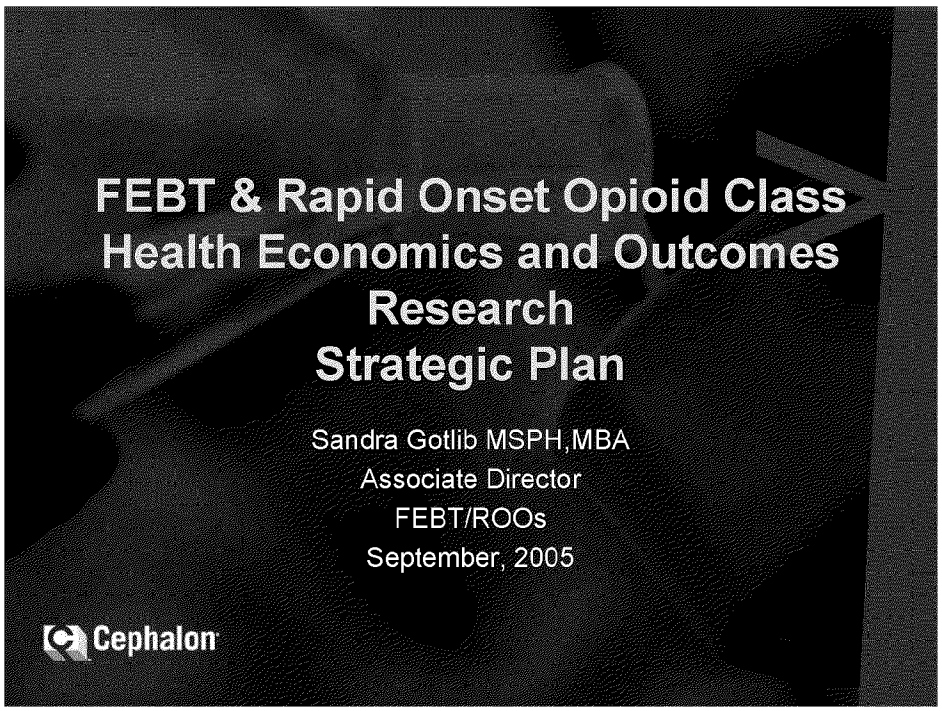
Appendix 7 – Palio Tactical Time Line

NOTE: Please refer to ISCP website for electronic version



Appendix 8 – Health Economic Outcomes Research Plan

NOTE: Please refer to ISCP Web site for full presentation.



Appendix 9 – Integrated Strategic Communication Plan

OraVescent Technology			
OraVescent Technology Overview	OraVescent is a breakthrough drug delivery technology utilizing effervescence in a tablet for rapid, efficient transport of active drug across the buccal mucosa	• Effervescent buccal tablets deliver drug faster and more efficiently than traditional oral delivery and conventional oral transmucosal delivery systems (eg, lozenge and sublingual delivery) (Pather 2001) • Efficient transport of active drug across the buccal mucosa minimizes first-pass metabolism (Fukodo 2005)	• OraVescent technology has potential applications in highly lipophilic compounds • OraVescent technology has potential applications in compounds that are weakly basic
Effervescence	OraVescent technology optimizes drug delivery through an effervescence reaction (Pather 2001)	• OraVescent buccal tablets employ effervescence to bring about a dynamic pH shift that enhances dissolution and optimizes the speed and extent of drug absorption. (Pather 2001)	• Patient places OraVescent tablet in the buccal cavity, where saliva causes an immediate effervescence reaction (Pather 2001) • During effervescence, the nontoxic citric acid and sodium bicarbonate in OraVescent form carbonic acid (Pather 2001) • Carbonic acid drives down the pH, enhancing dissolution of the ionized form of the drug (Pather 2001) • Carbonic acid dissociates into carbon dioxide and water. The carbon dioxide bubbles out of the saliva or passes across the

			mucosa (Pather 2001) • The loss of carbon dioxide represents a loss of acid in the system, which now contains an excess of bicarbonate. This raises the pH and causes the ionized form of the drug to become un-ionized, favoring absorption (Pather 2001) • Carbon dioxide has been hypothesized to have an effect on epithelial permeability. Preclinical research suggests that carbon dioxide may promote drug absorption by altering the paracellular pathway (Eichmann 1998)
Ease of Use	OraVescent buccal tablets offer discreet, convenient self-administration for patients	• Simplified self-administration without water • Discreet dosage form may improve patient compliance	• OraVescent buccal tablets dissolve passively in the mouth without the need for active administration

Chronic Pain			
Definition of Chronic Pain	Chronic pain is pain that lasts beyond the expected time for healing of an injury or insult (>3 months) (National Pharmaceutical Council 2005)		
Components of Chronic Pain	Chronic pain typically has 2 components: persistent pain and breakthrough pain (BTP) (American Cancer Society 2005)	• Persistent pain is baseline pain that is continuous throughout the day • BTP is a transitory exacerbation, or flare, of moderate-to-severe pain that occurs in patients with otherwise stable persistent pain (Portenoy 1990, Mercadante 2002)	
Prevalence of Chronic Pain	About 50 million of the estimated 75 million Americans who live with "serious pain" suffer from chronic pain (American Pain Foundation 2005)		
Categories and Characteristics of Chronic Pain	Chronic pain has traditionally been categorized as a symptom of other diseases (eg, cancer), but current thinking recognizes it as a distinct disease state	• Chronic pain may be caused by injury (eg, trauma, surgery), malignant conditions, or a variety of chronic non-life-threatening conditions (eg, arthritis, fibromyalgia, neuropathy) (National Pharmaceutical Council 2005) • Chronic pain may be continuous or intermittent with or without acute exacerbations (National Pharmaceutical	• Chronic pain may be nociceptive, neuropathic, or mixed (National Pharmaceutical Council 2005) • Nociceptive pain arises from the stimulation of pain receptors (nociceptors) when body tissues are damaged (Douglass 2005) • Neuropathic pain occurs when nerve pathways are damaged or function

		Council 2005) • The biochemical mechanisms of the sensation of pain are the same in cancer and noncancer chronic pain conditions (Turk 2002)	abnormally. It can occur independently of nociceptive pain or in conjunction with it (Douglass 2005)
Diagnosis and Treatment of Chronic Pain	Chronic pain is complex and may be comprised of 2 components, persistent pain and BTP (American Cancer Society 2005). Each component requires independent assessment and targeted treatment (Bennett 2005b)	• Diagnosing and managing chronic pain requires a substantial time commitment • The medical community has not reached consensus on optimal diagnosis and treatment guidelines • Persistent pain is typically managed with around-the-clock (ATC) medications (Bennett 2005b) • Some physicians avoid prescribing scheduled medications (eg, opioids) due to fears of abuse, diversion, or regulatory scrutiny (Savage 1996)	
Economic Impact of Chronic Pain	Chronic pain has a significant economic impact on patients and society	• Annual US cost of pain-related lost productivity, including absence, is approximately $61.2 billion (Stewart 2003) • Almost 50% of Americans seek medical care each year for pain, making pain the single most frequent reason for a physician consult in the United States (Bennett 2005a)	• In one study, 76% of patients with cancer experienced at least one pain-related expense (average: $891/month) (Fortner 2003)
Physical and Psychosocial Impact of Chronic Pain	Chronic pain disrupts sleep and normal living, ceases to serve a protective function, and, instead, degrades health and functional capability	• Pain is associated with feelings of frustration, bitterness, and anxiety, which are common for both the patient and his or her family (McNeely 2000) • Chronic pain is	• Chronic pain has a negative effect on physical and psychosocial well-being, including mood, sleep, and ability to work or enjoy activities

	(National Pharmaceutical Council 2005)	associated with irritability, social withdrawal, depressed mood and vegetative symptoms (eg, changes in sleep, appetite, libido), disruption of work, and social relationships capability (National Pharmaceutical Council 2005)	(Caldwell 1999)
[redacted]			
Breakthrough Pain			
Definition of BTP	BTP is a transitory exacerbation, or flare, of moderate-to-severe pain that occurs in patients with otherwise stable persistent pain (Portenoy 1990, Mercadante 2002)		
Characteristics of BTP	• Onset of BTP is rapid, with escalation to maximum intensity in as little as 3 minutes (Portenoy 1990, Portenoy 1999) • BTP is often of moderate-to-severe intensity (Zeppetella 2000) • Approximately 40% to 50% of BTP episodes are unpredictable (Bennett 2005a) • The average duration of a BTP episode is 30 to 60 minutes (Portenoy 1990, Fine 1998, Portenoy 2005, Simon 2005, Bennett 2005c) • The average	• Episodes of BTP are often unpredictable. For episodes that are predictable, it is nearly impossible to predict duration or time to peak severity (Hwang 2003, Bennett 2005a)	

	number of BTP episodes is 2 to 4 per day (Portenoy 1990)		
Categories of BTP	Evidence has shown that BTP occurs in patients with both cancer and noncancer chronic pain	• BTP in patients with cancer is well recognized and well defined • BTP in patients with noncancer chronic pain, though less well studied, has been shown to have similar characteristics to BTP in patients with cancer	• BTP can be categorized as idiopathic, incident/predictable, incident/unpredictable, or end-of-dose failure
Prevalence of BTP	Up to 64% of patients with chronic cancer pain and 74% of patients with chronic noncancer pain experience breakthrough pain (Portenoy 1990, Portenoy 2005)		
Recognition of BTP	BTP is underrecognized due to a lack of validated assessment tools, adequate treatment guidelines, and education	• Physicians have no validated chronic pain assessment tool that includes a specific evaluation for BTP • Current pain treatment guidelines have only limited recognition of BTP • Historically, the pain community has not stressed the importance of physician education on BTP	
Treatment of BTP	BTP requires independent assessment and targeted treatment	• Opioids are the primary pharmacological treatment for BTP (Bennett 2005b) • Despite the current BTP treatment paradigm (10%-20% of around-the-clock [ATC] opioid), data have shown no correlation between the dose of the ATC opioid medication and the	

		dose required to treat BTP (Christie 1998) • Increasing the dose of ATC pain medications to treat BTP often results in overmedication and increased side effects such as sedation, constipation, and confusion • While oral short-acting opioids (SAOs) are commonly used to treat BTP, their relatively slow onset of action makes them a poor fit for the rapid onset of BTP (Bennett 2005b) • The preferred BTP treatment would provide rapid analgesia and a duration of effect that matched a typical BTP episode. This profile could be offered by a lipophilic rapid onset opioid (ROO)	
Economic Impact of BTP	BTP has a significant economic impact on patients and society	• Among patients with cancer, total annual cost of pain-related hospitalizations and physician office visits was 5 times greater for patients with BTP than for patients without BTP ($12,000 vs $2,400) (Fortner 2002) • Among patients with cancer, those with BTP are 2.5 times more likely to seek care in an emergency department than those without BTP (Fortner 2002) • Among patients with cancer, those with BTP experience 2.5 times more hospitalizations per year than those without BTP (1.0 vs 0.4) (Fortner 2002)	• Among patients with cancer, those with BTP have higher direct pain-related costs than those without BTP ($1,080/year vs $750/year) (Fortner 2003)
Physical and Psychosocial Burden	BTP has been associated with	• BTP has been shown to predict poor medical outcomes in patients	

of BTP	functional impairment and psychological distress (Portenoy 1999, Goudas 2005)	with cancer, and is associated with significant patient morbidity, decreased functioning, and increased levels of anxiety and depression (Bennett 2005a, Caraceni 2004, Portenoy 1999)	
[redacted]			
Rapid Onset Opioid (ROO)			
Definition of ROO	A rapid onset opioid (ROO) is an opioid with an onset of analgesia of 15 minutes or less	• Short-acting opioids (SAOs) have an onset of analgesia of 30 to 40 min (Bennett 2005b)	
Classification of ROO	ROOs are an emerging subclassification of pain medications based on onset, rather than duration of analgesia *Note: "Key drug type" to be used in communication to managed care*	• The current opioid classification is based on duration of analgesia, either long acting or short acting, with no differentiation based on onset of analgesia • Due to the number of rapid onset products in development and their unique benefit profile, further subclassification of opioids based on onset of analgesia is emerging	• ROOs may have a different risk profile than SAOs, suggesting the need for further research • Appropriate patient selection and education may be required when prescribing ROOs
Efficacy	The ROO efficacy profile (rapid onset, moderate duration) closely matches the characteristics of a typical BTP episode, thereby providing a more appropriate treatment option than conventional SAOs		
[redacted]			

Pain Franchise			
Breakthrough Technology	Cephalon is applying breakthrough technologies to the challenges of pain management	• Applied oral transmucosal lozenge for delivery of fentanyl (OTFC) • Applied OraVescent technology for rapid delivery of fentanyl (FEBT)	
Innovative Treatments	Cephalon is delivering innovative treatments for pain	• Commercialized OTFC (ACTIQ) in the US market • Preparing to introduce fentanyl effervescent buccal tablet (FEBT) in the US market	
Pain Education	Cephalon is advancing the understanding of pain	• Introduced industry-leading risk management program for OTFC (ACTIQ) • Sponsor of numerous educational activities and forums on pain management to assist in educating patients and physicians	

For internal use only to standardize communications. Suggested but not required.

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Appendix 10 – Market Research Plan

FEBT Market Research Plan

Prelaunch

Study Name	Time
ISCP medical terminology + OV message	Q3 '05
Pain franchise image + message study	Q3 '05
FEBT branding elements	Q3 '05
BTP awareness testing (ad boards)	Q3 '05
Psychographic BTP patient study	Q3 '05
Promotional response	Q4 '05
FEBT message testing	Q4 '05
Pricing analysis	Q4 '05
FEBT final concept testing	Q1 '06
Baseline ATU	Q2 '06

Postlaunch (tentative research plan)

Study Name	Time Postlaunch
Weekly data trend analysis	Ongoing from launch
Managed care data tracking	Ongoing from launch
Diary study (current treatment patterns)	Ongoing from launch
Sales force effectiveness (5 monthly waves) - Message recall - Competitive response - Believability - Awareness - Penetration	2 months
ACTIQ loyalist switching study	3 months
Campaign tracking	6 months
Patient chart audit	3 quarters

Appendix 11 – Miscellaneous Tables and Charts

Table 1

Product Conversion Analogs Analysis

The products included in the conversion analysis are listed in the table below:

				Switch Rates[1]	
Product	**Precursor**	**Product Indication(s)**	**Time to Switch**	**5 months**	**10 months**
Adderall XR	Adderall	• ADHD	• 4 months	54%	74%
Clarinex	Claritin	• Allergies	• 12 months	42%	43%
Detrol LA	Detrol	• Incontinence	• Detrol patent expires 2012	38%	67%
Lexapro	Celexa	• Depression, anxiety	• 18 months	30%	63%
Nexium	Prilosec	• GERD, erosive esophagitis	• 20 months	14%	31%
Paxil CR	Paxil	• Depression, anxiety	• 18 months	11%	25%
Prozac Weekly	Prozac	• Depression	• 5 months	5%	5.5%
Sarafem	Prozac	• Premenstrual dysphoric disorder	• 12 months	2%	5%
Mean				*24.5%*	*39.2%*

[1] This is the TRx of the successor product as a percentage of the average precursor prescriptions 6 months before the launch of the successor.

Note: Switch rates alone are not indicative of the quality of a company's marketing tactics. For example, Adderall XR was able to achieve a high switch rate given Adderall's fairly low annual sales ($250 million in 2000) and the high market demand for a once-daily for ADHD.

Nexium/Prilosec's rate is not the highest because of Prilosec's significant sales volume (>$4 billion in 2000) and relatively low immediate demand for a new proton pump inhibitor.

Table 2

Breakthrough Pain – First-Line Therapy

		Low/Non Users			
	Heavy/Med Users of ACTIQ	**Non-ACTIQ Users**	**Pain Specialists**	**PCP**	**Other**
Moderate BTP pain					
Hydrocodone	65%	67%	77%	72%	59%
Oxycodone + acetaminophen	52%	26%	44%	28%	23%
Oxycodone	46%	17%	37%	14%	20%
ACTIQ	30%	6%	17%	6%	5%
Short-acting morphine	29%	12%	19%	10%	13%
Propoxyphene napsylate	25%	21%	27%	19%	22%
Acetaminophen + codeine	24%	27%	22%	31%	22%
Hydromorphone	15%	10%	11%	10%	9%
Severe BTP pain					
Oxycodone	57%	28%	51%	27%	27%
ACTIQ	55%	9%	28%	8%	7%
Oxycodone + acetaminophen	48%	37%	56%	35%	37%
Hydrocodone	41%	48%	48%	49%	46%
Short-acting morphine	36%	26%	28%	29%	23%
Hydromorphone	32%	17%	24%	17%	18%
Acetaminophen + codeine	16%	16%	14%	19%	12%
Propoxyphene napsylate	13%	12%	17%	14%	9%

Blue = combination SAO Yellow = pure SAO White = respondent did not specify type of SAO

Source: Pain Market Dynamics Study, March 2005.